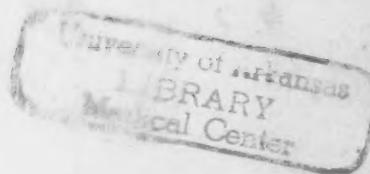


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August, 1960

Volume 80, number 2

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American Journal of OBSTETRICS AND GYNECOLOGY

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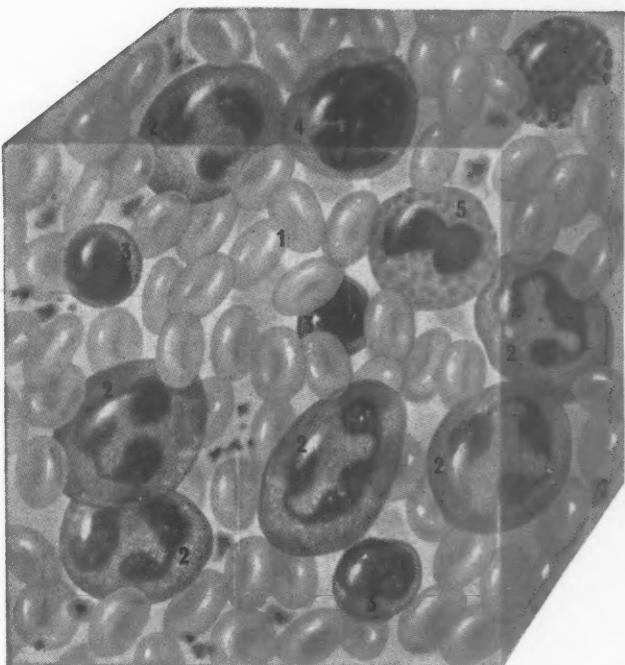
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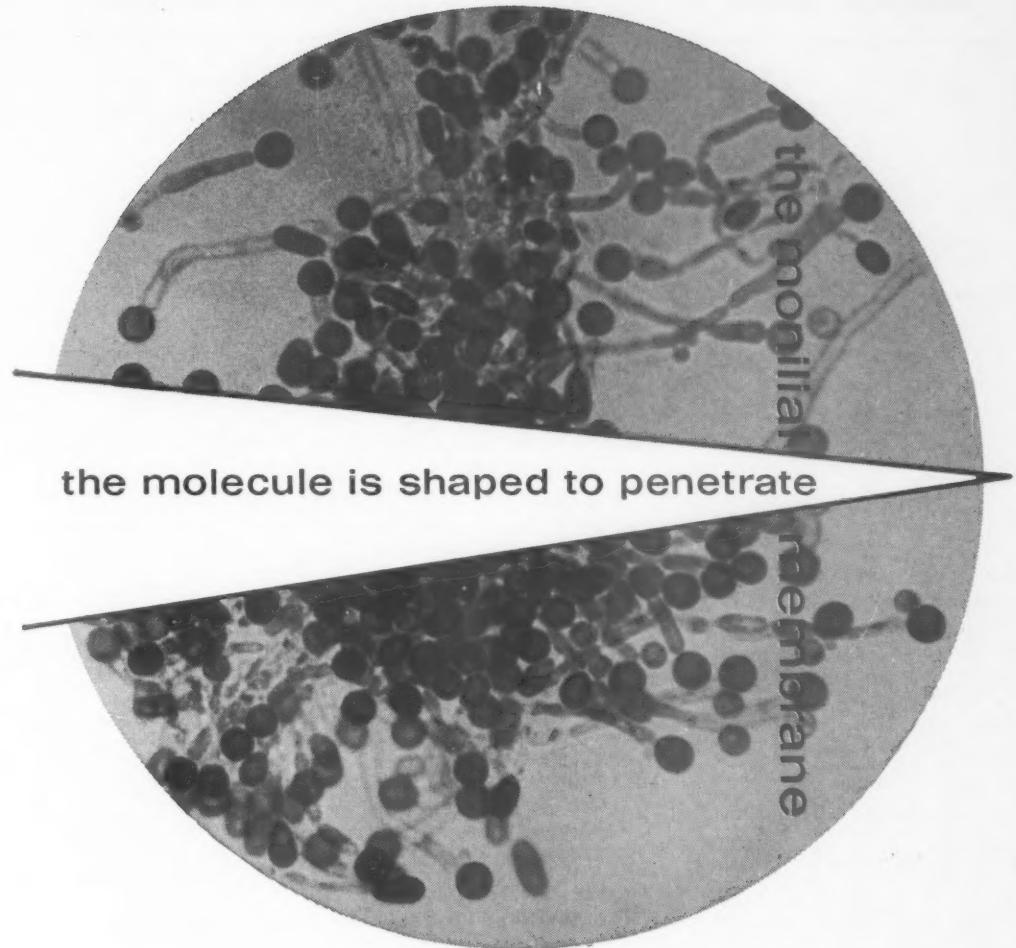
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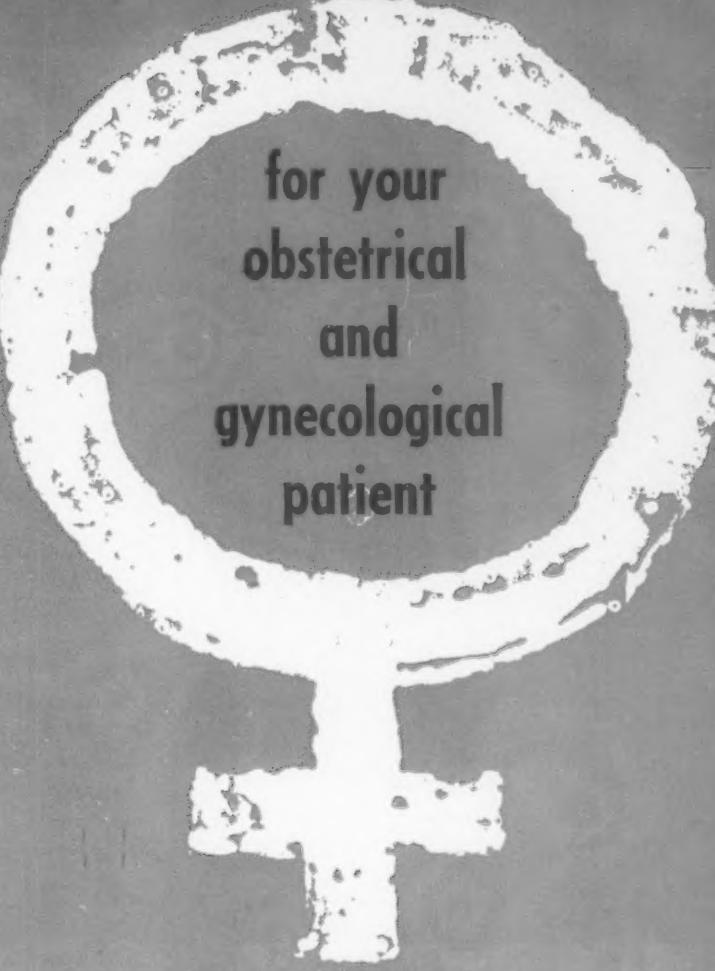
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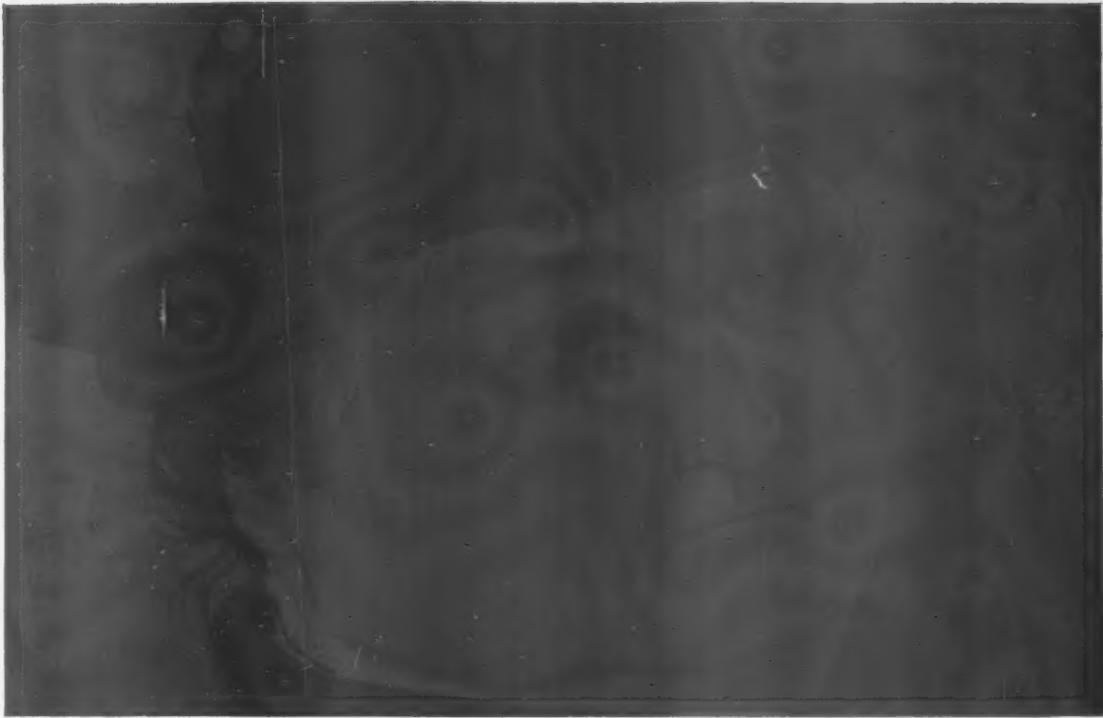
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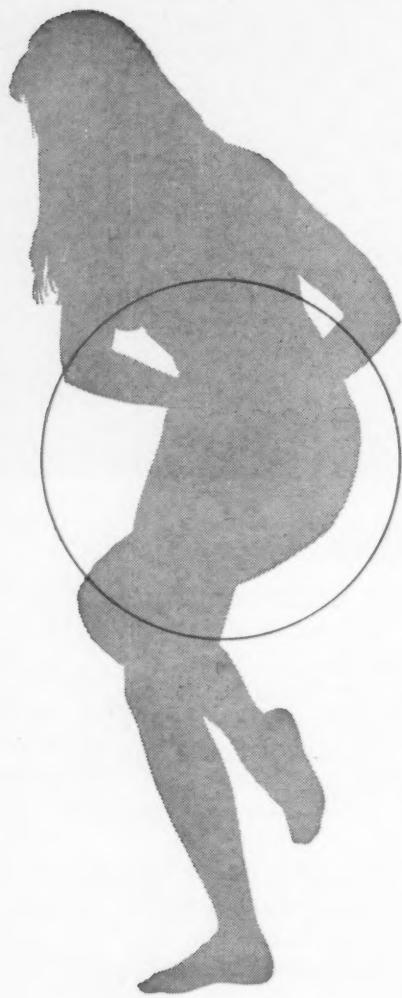
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Gentian violet is the most effective agent known for the destruction of *Monilia albicans*. Numerous nonstaining preparations have been used in treating vaginal monilliasis but have proven far less effective than gentian violet.

Gentia-jel's effectiveness is proved by its rate of cures during the last trimester of pregnancy, when mycotic infections are most difficult to cure. Gentia-jel is shown to be over 93% clinically effective, and has been used successfully in hundreds of cases refractory to other therapies.

Monilial reinfection is avoided with Gentia-jel by eliminating two major causes: (1) there is no manual introduction of tablets or suppositories into the vagina and (2) applicators are never reused, but discarded.

And, Gentia-jel is easy for your patients to use. (1) Prior to retiring for the night, patients lie back with knees flexed, insert applicator and instill Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or peldorf of cotton is inserted in the introitus. A sanitary pad should be worn.

Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators.



**WHY WAIT UNTIL OTHER THERAPIES FAIL...
START YOUR PATIENTS WITH GENTIA-JEL**

WESTWOOD PHARMACEUTICALS

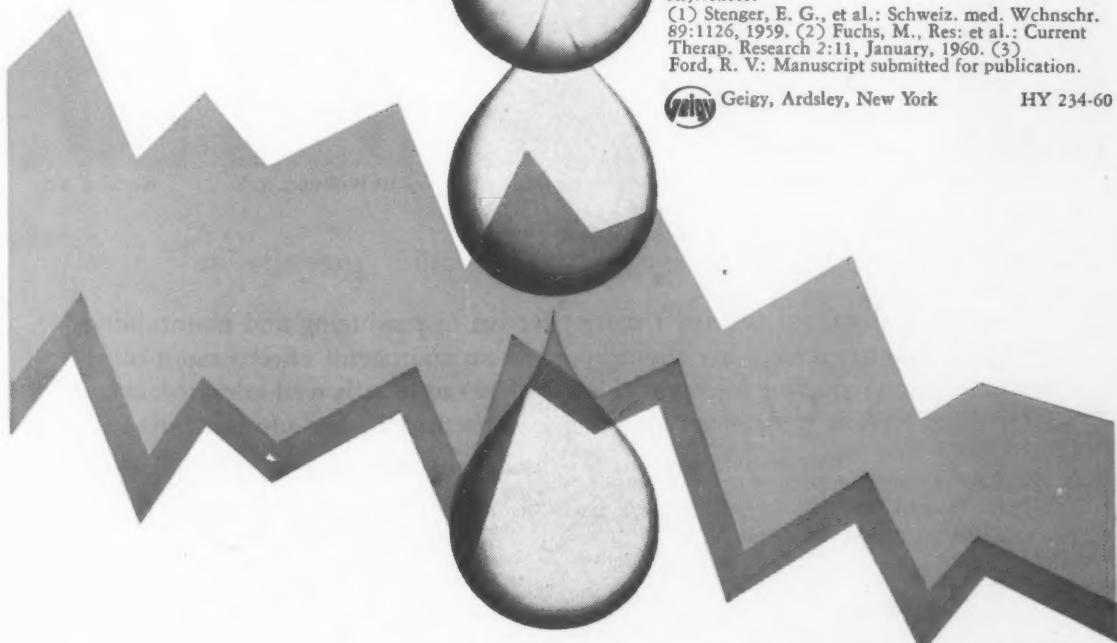
Buffalo 13, New York

New Hygroton® Geigy

brand of chlorthalidone

longest in action... smoothest in effect

in hypertension and edema



greater loss of sodium
lesser loss of potassium

A new antihypertensive-saluretic, Hygroton, now enables still more effective control of hypertension and edema.

more evenly sustained therapeutic response
Because it is more prolonged in action than any other diuretic,¹ Hygroton affords a smoother, more evenly sustained response.

more nearly pure natriuretic effect
Hygroton produces only minimal potassium loss . . . affords a better sodium-potassium ratio than other saluretics.³

more liberal diet for the patient
As a rule, with Hygroton, restriction of dietary salt is unnecessary.

more convenience and economy
For maintenance therapy three doses per week suffice to manage the vast majority of cases.²

In arterial hypertension
Sustained control without side reactions.

In edematous states
Copious diuresis without electrolyte imbalance.

Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100.

References:
(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication.



Geigy, Ardsley, New York

HY 234-60

Each of the babies pictured on this page was borne by a mother with a *documented* previous history of true habitual abortion, who was treated with DELALUTIN during the pregnancy leading to this birth

LIVING PROOF OF FETAL SALVAGE WITH **DELALUTIN**

SQUIBB HYDROXYPROGESTERONE CAPROATE

Improved Progestational Therapy



Garden City, N. Y.



Skokie, Ill.



Denver, Colo.



No. Massapequa, L. I., N. Y.



Roselle, Ill.



Seaford, N. Y.



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East Williston, N. Y.



Norwich, Vt.

DELALUTIN offers these advantages over other progestational agents

- long-acting sustained therapy • more effective in producing and maintaining a completely matured secretory endometrium • no androgenic effect • more concentrated solution requiring injection of less vehicle • unusually well-tolerated, even in large doses • fewer injections required • low viscosity makes administration easy

Complete information on administration and dosage is supplied in the package insert

Supply: Vials of 2 and 10 cc., each containing 125 mg. of hydroxyprogesterone caproate in benzyl benzoate and sesame oil.

SQUIBB



Squibb Quality—The Priceless Ingredient

*DELALUTIN® IS A SQUIBB TRADEMARK

by every
standard
the drug for
"morning sickness"

Bonine®

brand of meclizine hydrochloride



IN BRIEF

BONINE is an antiemetic which provides rapid and prolonged protection against nausea and vomiting due to a variety of causes. A single dose of **BONINE** is usually effective for 24 hours. Thus, **BONINE** can be taken at bedtime to help prevent "next morning" sickness.

INDICATIONS: Valuable in the symptomatic relief of nausea and vomiting of pregnancy. Also indicated for motion sickness, radiation sickness, vertigo associated with Ménière's syndrome, labyrinthitis, fenestration procedures, vestibular dysfunction, and dizziness associated with cerebral arteriosclerosis.

ADMINISTRATION AND DOSAGE: For control of nausea and vomiting of pregnancy, a daily dose of 25 to 50 mg. is usually effective. For dosage schedules in other indications, see package insert.

SIDE EFFECTS: Not a phenothiazine, the side effects reported in association with Bonine have been mild and/or transient and consist of occasional drowsiness, dryness of the mouth, and blurred vision. Drowsiness is seen less frequently with **BONINE** in therapeutic dosages than with most other effective antiemetics.

PRECAUTIONS: As with other antihistaminic compounds, the physician should inform patients of the need for caution in driving a car or when engaged in other activities requiring alertness. There are no known contraindications to **BONINE**.

SUPPLIED: **BONINE** Tablets, scored, tasteless, 25 mg. **BONINE** Chewing Tablets, mint-flavored, 25 mg. **BONINE** Elixir, cherry-flavored, 12.5 mg. per teaspoonful (5 cc.).

More detailed professional information available on request.

"life
saving"
in many cases...

KANTREX®

INJECTION

Kanamycin Sulfate Injection

...a highly potent, bactericidal antibiotic for combating staph and gram negative infections

"There appears to be no doubt that kanamycin has been lifesaving in those instances in which organismal resistance precludes the use of other antimicrobials."* Well tolerated when used on a properly individualized dosage schedule which does not induce excessive blood levels.

*Council on Drugs, J.A.M.A., 172:699, 1960.

Information on dosage, administration and precautions contained in official package circular, or available on request.

SUPPLY: KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in vial containing 2 ml. volume. KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in vial containing 3 ml. volume.

BRISTOL LABORATORIES, SYRACUSE, NEW YORK

CPL-1822

New!...
for
appetite
control



Controls compulsive overeating

CURBS APPETITE... RELIEVES TENSION HUNGER...
TRANQUILIZES "DIET JITTERS"

Why do so many overweight patients so often break their diets?

The reason is usually tension.^{1,2,3} Now—Appetrol has been formulated to help you solve this problem.

Appetrol provides dextro-amphetamine to curb your patient's appetite. Even more important, it provides meprobamate to control compulsive overeating, to ease the frustration of the dietary regimen—and to minimize the jittery effects of amphetamine.

Usual dosage: 1 or 2 tablets one-half to 1 hour before meals. Each tablet contains: 5 mg. dextro-amphetamine sulfate and 400 mg. meprobamate.

Available: Bottles of 50 pink, scored tablets.

Thus, Appetrol does more than other anorectics which merely suppress appetite. Appetrol also tranquilizes tension hunger to give more complete control of compulsive overeating. Your patients find it easier to stay on their diets—even during prolonged periods.

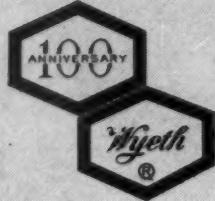
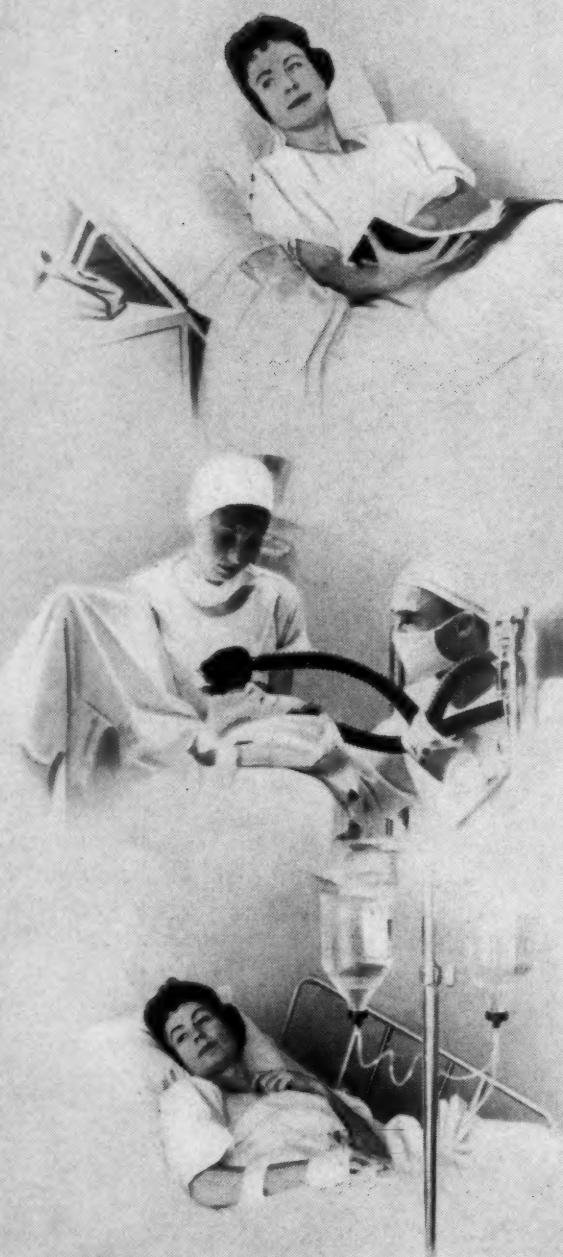
References: 1. Freed, S. C.: Psychic factors in the development and treatment of obesity. *J.A.M.A.* 133:369, Feb. 8, 1947. 2. Kotkov, B.: Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, Oct. 1958. 3. Plotz, M.: Modern management of obesity—the "social diet." *J.A.M.A.* 170:1513, July 25, 1959.

Appetrol®
DEXTRO-AMPHETAMINE + MEPROBAMATE
for appetite control



WALLACE LABORATORIES / New Brunswick, N. J.

Premedication plus benefits in surgery



A Century of Service to Medicine

before...

relaxes patient, induces light sleep, prevents and controls vomiting.

during...

permits reduced amounts of anesthetics; controls vomiting, hiccups and reflex irritability.

after...

reduces analgesic requirements and provides antiemetic and sedative benefits.

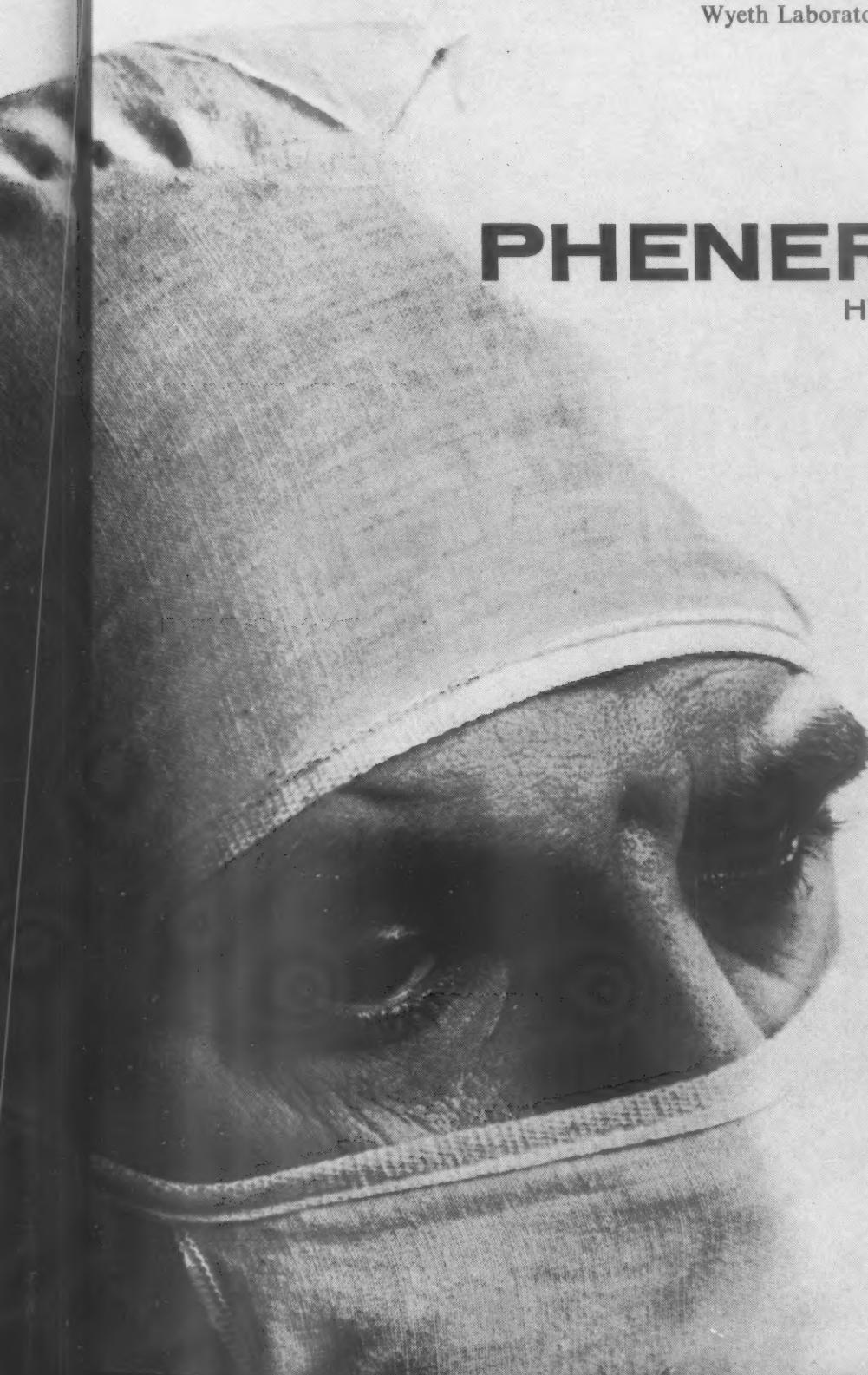
Comprehensive literature supplied upon request.
Wyeth Laboratories Philadelphia 1, Pa.

INJECTION
TABLETS
SYRUP
SUPPOSITORIES

PHENERGAN®

HYDROCHLORIDE

Promethazine
Hydrochloride,
Wyeth



In trichomonas vaginitis
"...permanent **CURES** in
84.6%"¹ ■ "...symptomatic
and bacteriologic **CURES**"
in 100%² ■ "symptomatic **CURE**
was obtained in 100%, and
bacteriologic **CURES** in 82.5%"³
in moniliasis "symptomatic **CURE**
was effected in about 80%"⁴
in mixed infections "complete
symptomatic and bacteriologic
CURES in 92%"⁵
in endocervicitis 75% "were
clinically and bacteriologically
(as indicated by vaginal
smears and cultures) **CURED**"⁵

AVC IMPROVED CREAM/SUPPOSITORIES

STOPS THE TORMENT DESTROYS THE CAUSE

CURES

Vaginitis (trichomonal, monilial, nonspecific), Cervicitis

References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.



Products of Original Research

THE NATIONAL DRUG COMPANY Philadelphia 44, Pa.

Trademark: AVC AVC-739/60

women of childbearing age...
and growing children...

are
depleting their
iron
reserves

Iron deficiency anemias occur most often among women of childbearing age and growing children. Unless extra iron is provided, children's high growth requirements and women's iron loss from menstruation may dangerously deplete iron reserves. Many clinicians regularly prescribe a hematinic for six weeks each year during a woman's reproductive years. Children and adolescents are kept on intermittent iron therapy.

Livitamin, with peptonized iron and B complex, provides effective iron therapy with minimal side effects. Unlike many hematinics, Livitamin is pleasant tasting and well tolerated. Peptonized iron has as high a rate of absorption and storage, and is much less irritating than ferrous sulfate. B complex and other ingredients provide integrated nutritional support.

LIVITAMIN®

with Peptonized Iron

FORMULA: Each fluidounce contains:

Iron peptonized 420 mg.
(Equiv. in elemental iron
to 71 mg.)
Manganese citrate, soluble 158 mg.
Thiamine hydrochloride 10 mg.
Riboflavin 10 mg.
Vitamin B₆ Activity 20 mcg.
(Derived from Cobalamin conc.)

SUPPLIED IN LIQUID OR CAPSULE

Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

THE S. E. M ASSENGILL COMPANY

Bristol, Tennessee • New York
Kansas City • San Francisco

*Patients prefer Livitamin
because it is highly
palatable
and
non-irritating.*

Clinical studies
show peptonized iron
has these advantages:*

- Rapid response in iron-deficiency anemias
- Non-astringent
- Absorbed as well as ferrous sulfate
- Better gastric toleration than ferrous sulfate
- Less constipating than ferrous sulfate

LIVITAMIN®

*with
Peptonized
Iron*

... the preferred
hematinic

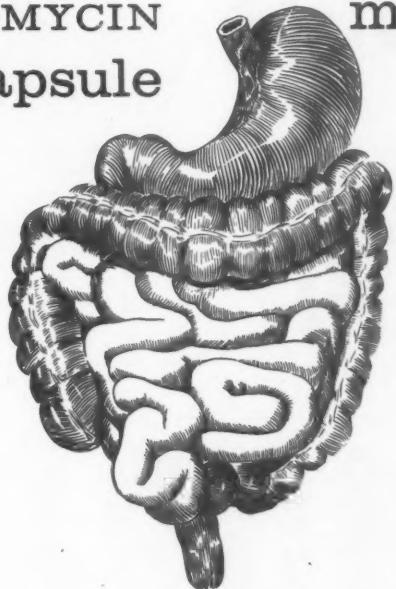
*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

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DECLOMYCIN NOTES:

Demethylchlortetracycline Lederle

antibiotic
toleration
reduction in incidence and/or severity of gastrointestinal side effects may be attributed to the far lower
DECLOMYCIN milligram intake
(per capsule) ⁽¹⁻³⁾
and per day)



1. Finland, M.; Hirsch, H. A., and Kunin, C. M.: Observations on Demethylchlortetracycline. Presented at Seventh Annual Antibiotics Symposium, Washington, D. C., November 5, 1959.
2. Hirsch, H. A.; Kunin, C. M., and Finland, M.: Demethylchlortetracycline -A New and More Stable Tetracycline Antibiotic That Yields Greater and More Sustained Antibacterial Activity. München. med. Wochschr. To be published.
3. Lichter, E. A., and Sobel, S.: The Distribution of Oral Demethylchlortetracycline in Healthy Volunteers and in Patients Under Treatment for Various Infections. To be published.

Capsules, 150 mg.—Pediatric Drops, 60 mg./cc.—Oral Suspension, 75 mg./5 cc. tsp.

GREATERT ACTIVITY...FAR LESS ANTIBIOTIC...UNRELENTING-PEAK CONTROL..."EXTRA-DAY" PROTECTION AGAINST RELAPSE
LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, N.Y.

in edema of pregnancy

"gratifying relief..."

in all patients

treated with



HYDRO DIURIL®

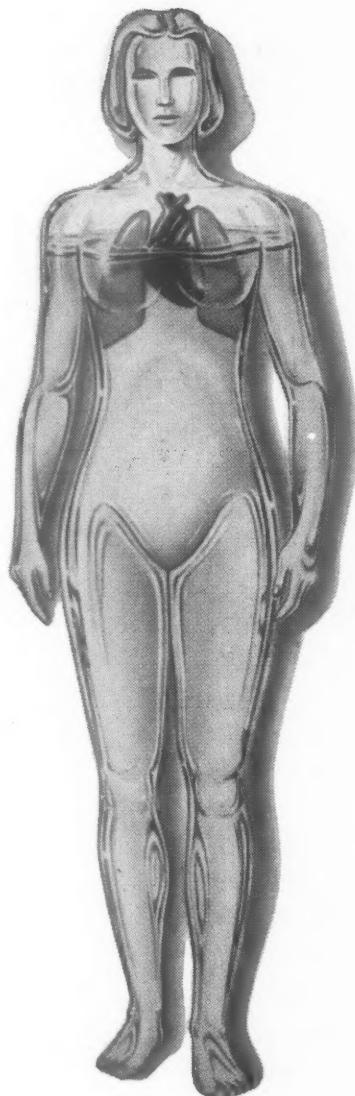
HYDROCHLOROTHIAZIDE

increased potency—without corresponding increase in side effects

Ford, Ralph V.: Southern Med. Jl. 52: 40, (Jan.) 1959

"Hydrochlorothiazide was given to patients with edema (mild to moderate) of varied etiology..."

"There were...5 women in the third trimester of pregnancy." In these patients the cumulative weight loss was 2 pounds after seven days of therapy and 4 pounds after twenty-one days. Gratifying relief of edema was observed in all patients.



DOSAGE: One or two 50 mg. tablets HYDRODIURIL once or twice a day, depending upon the condition and individual patient response.

SUPPLIED: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) in bottles of 100 and 1,000.

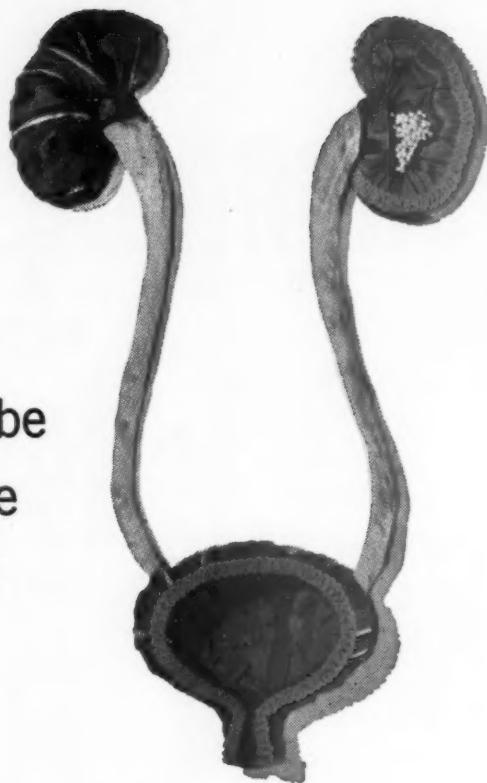
HYDRODIURIL is a trademark of Merck & Co., INC.

Additional information on HYDRODIURIL is available to the physician on request. ©1960 Merck & Co., INC.



MERCK SHARP & DOHME
Division of Merck & Co., Inc. Philadelphia 1, Pa.

Just a "simple" case of cystitis may be the precursor of pyelonephritis¹—or may actually be the first evidence of a pre-existing pyelonephritic process.²



WHEN TREATING CYSTITIS—SPECIFY

FURADANTIN®

brand of nitrofurantoin

FIRST
to ensure rapid control of infection
throughout the urogenital system

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, Proteus and certain strains of Pseudomonas, resistant to other agents

- actively excreted by the tubule cells in addition to glomerular filtration
- negligible development of bacterial resistance after 8 years of extensive clinical use
- excellent tolerance—nontoxic to kidneys, liver and blood-forming organs
- safe for long-term administration

AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. q.i.d. with meals and with food or milk on retiring. Supplied: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

NITROFURANS—a unique class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

**WHEN
PROGESTERONE THERAPY
IS INDICATED...**

Indications: amenorrhea • functional uterine bleeding • endocrine infertility • habitual abortion • threatened abortion • dysmenorrhea • premenstrual tension

Packaging: 5-mg. scored tablets, bottles of 30.

PARKE, DAVIS & COMPANY
Detroit 32, Michigan

PARKE-DAVIS

NORLUTIN®

(norethindrone, Parke-Davis)

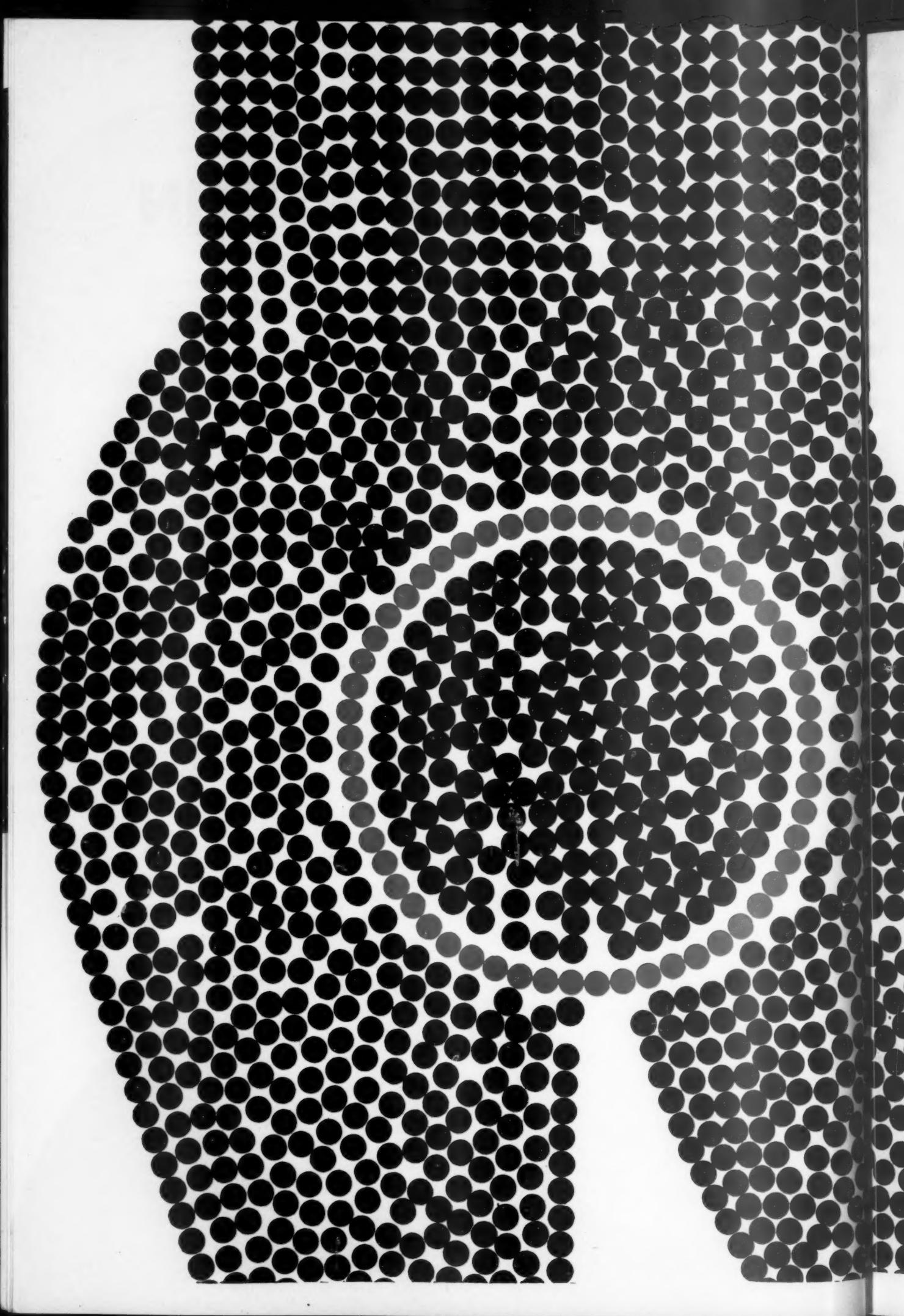
ORAL PROGESTATIONAL AGENT

In gynecologic hormonal disorders, NORLUTIN is capable of producing a more physiological remedy than previously used progestogens or androgens by restoring the normal estrogen-progestogen ratio.*

* Bishop, P. M. F.: *Brit. M. J.* 1:184, 1960.

36040





CONSISTENT RESPONSE IN VAGINITIS

UNREMITTING THERAPY FOR PERSISTENT SYMPTOMS

85% SUCCESS:^{1,2} TRIBURON VAGINAL CREAM
ACHIEVED SYMPTOMATIC CONTROL IN 109 OF 128
WOMEN WITH TRICHOMONAL, MONILIAL AND NON-
SPECIFIC VAGINITIS. PARTICULARLY GOOD RESULTS
WERE OBTAINED IN TRICHOMONAL AND MIXED
INFECTIONS, AND ONLY TWO INSTANCES OF TRANSIENT
BURNING OCCURRED. OF 106 CASES FOLLOWED FOR
THREE MONTHS, ONLY 11 RECURRENCES WERE NOTED.

IN ONE STUDY, TRIBURON VAGINAL CREAM
DEMONSTRATED "DEFINITE ADVANTAGES"¹ OVER
OTHER PREPARATIONS: HIGH ANTIBACTERIAL AND
ANTITRICHOMONAL EFFECTS, RAPID DIFFUSION,
PROLONGED RETENTION. FURTHER, THE ACTIVE
COMPONENT OF TRIBURON VAGINAL CREAM,
TRICLOBISONIUM CHLORIDE, HAS BEEN PROVED
"NON-IRRITATING...NOT SENSITIZING."²

TRIBURON VAGINAL CREAM FOR VULVITIS AND
VAGINITIS DUE TO TRICHOMONAS VAGINALIS,
CANDIDA ALBICANS, HEMOPHILUS VAGINALIS AS
WELL AS MIXED INFECTIONS; AFTER CAUTERIZATION,
CONIZATION AND IRRADIATION; FOR SURGICAL
AND POSTPARTUM TREATMENT. THERAPY MAY BE
CONTINUED DURING PREGNANCY AND MENSTRUATION.

HIGHLY ACCEPTABLE TO PATIENTS

TRIBURON VAGINAL CREAM—A SMOOTH, WHITE,
NONSTAINING PREPARATION WITH NO HINT OF
MEDICINAL ODOR—HAS THE ADVANTAGES
OF CONVENIENT BEDTIME ADMINISTRATION AND
OF DISPOSABLE APPLICATORS.

SUPPLIED: 3-OUNCE TUBES WITH 18 DISPOSABLE APPLICATORS.

REFERENCES: 1. N. MULLA AND J. J. McDONOUGH, ANN. NEW YORK ACADE. SC., 82:
(ART. 1), 182, 1959. 2. L. E. SAVEL, D. B. GERSHENFELD, J. FINKEL AND P.
DRUCKER, IBID., P. 186. 3. R. C. V. ROBINSON AND L. E. HARMON, ANTIBIOTICS
ANNUAL 1958-1959, NEW YORK, MEDICAL ENCYCLOPEDIA, INC., 1959, P. 113.
TRIBURON[®] CHLORIDE



ROCHE LABORATORIES

DIVISION OF HOFFMANN-LA ROCHE INC • NUTLEY 10, N. J.

Triburon

VAGINAL CREAM
decisive microbicidal therapy in a delicate matter
not an antibiotic • not a nitrofuran



NIAMID®

brand of nialamide

the mood brightener

...brightens dark days of the menopause

NIAMID has had excellent results during the menopause — easing difficult mental adjustment caused or complicated by depression. As the patient's attitude improves, she often takes more interest in her appearance and becomes more sociable.

NIAMID acts gradually, gently, without rapid jarring of physical or mental processes. The patient's family usually is first to notice her reawakening interest in life.

Although NIAMID has proved to be an unusually well tolerated antidepressant, the possibility of hepatic reactions should be kept in mind, especially where there is a history of liver disease.

More than 500,000 prescriptions in many clinical conditions—more than 90 published papers.

Supplied as 25 and 100 mg. scored tablets. Professional Information Booklet available on request from the Medical Department, Pfizer Laboratories, Brooklyn 6, N. Y.

Pfizer Science for the world's well-being™

Cystitis

*Responds
Rapidly
to Soothing,
Antiseptic*

URISED.[®]



Effective as individual therapy or as adjunctive medication in your regimen

SIMPLE, ACUTE or CHRONIC infections of the urinary tract are *safely* treated with URISED*. In 50 geriatric cases (average age 75½ years) Strauss reports¹ excellent to good results in 72%. No drug reactions occurred during prolonged therapy even though the majority of cases suffered from some form of chronic cardiac, vascular or neurologic disease.

New, additional evaluations confirm^{2,3} these findings.

Each Urised tablet contains: atropine sulfate 1/2000 gr.; hyoscyamine 1/2000 gr.; gelsemium, methenamine, methylene blue, benzoic acid, salol.

Rx URISED: Two Tablets, q.i.d.

REFS.: 1. Strauss, B., Clinical Med., 4:307-310, 1957; 2. Marshall, W., Clin. Med., Mar., 1960; 3. Haas, J., Pers. Com.

PAIN RELIEF IS PROMPT SINCE URISED:

- relaxes smooth muscle spasm, overcoming urinary retention,
- attacks infection with bacteriostatic-spasmolytic actions,
- effects results in either acid or alkaline media.

PHYSICIANS AND PATIENTS ARE INCREASINGLY GRATIFIED BECAUSE URISED:

- is safe, causes no undesirable reactions,
- prevents development of "resistant strains,"
- has no contraindications,
- IS ECONOMICAL.

*For generous free treatment table supplies of Urised startersamples, just mail the card with your name and address on the reverse side.

Postage
Will Be Paid
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No
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BUSINESS REPLY CARD
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Pleased Menopausal Patients are Routine with ESTROSED® Therapy

Estrogenic deficiencies and emotional disturbances are successfully managed with flexible, potent Estrosed.

- Vasomotor instabilities respond to ethinyl estradiol, ". . . one of the most potent estrogens known."¹
- Nervousness and insomnia are quieted with reserpine, ". . . useful chiefly for its psychotherapeutic sedative action in the symptomatic management of patients with anxiety or tension psychoneurosis . . ."²

Your results with Estrosed therapy will also be gratifying. Estrosed contains 0.01 mg. ethinyl estradiol and 0.1 mg. reserpine.

Low Dosage—Economical Therapy

Suggested dosage: one or two tablets once or twice daily for one week or until symptoms are controlled. For maintenance, one or two tablets daily or every other day.

1. N.N.R., 1959, 515 2. Ibid, 376

Chicago Pharmacal Co.
5547 N. Ravenswood Ave.
Chicago 40, Ill.

OG-JRL

Re: Please forward generous supplies of Urised Estrosed

Dr. _____

Address _____

City _____ State _____



For generous supplies of Estrosed and Urised for use as "starter treatments" fill out and return this card.



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PHARMACAL
COMPANY**

New

Enhances Vitality and Promotes Weight Loss

Prelu-Vite^{T.M.}

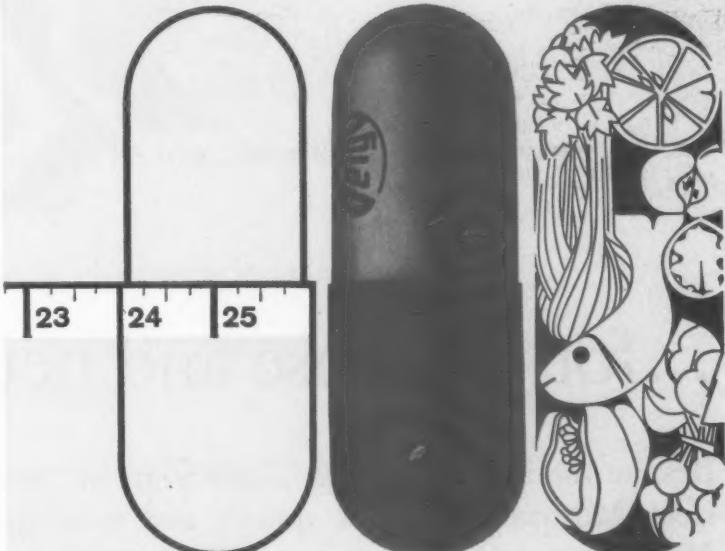
brand of phenmetrazine HCl with vitamins and minerals

Now, Prelu-Vite helps to fortify the patient's nutritional status and sense of well-being without jeopardizing the success of the weight-reducing program.

By improving nutritional status Prelu-Vite makes it easier for the patient to retain the initial zeal for reducing...facilitates the retention of enthusiastic cooperation in pursuing therapy to a successful conclusion.

With Prelu-Vite, as with Preludin, a weight loss 2-5 times that obtainable by dietary restriction alone, is readily achieved without the occurrence of annoying side reactions.

Geigy



Availability:

Prelu-ViteTM Capsules, each containing 25 mg. of Preludin (brand of phenmetrazine HCl) with vitamins A, B, C and D and 5 minerals.
Under license from C. H. Boehringer Sohn, Ingelheim.

Also available:

PreludinTM EnduretsTM-prolonged-action tablets (75 mg.) for once daily administration; and as regular Preludin tablets (25 mg.) for b.i.d. or t.i.d. administration.

Geigy, Ardsley, New York



321-60

In over five years



...for the tense and nervous patient

Despite the introduction in recent years of "new and different" tranquilizers, Miltown continues, quietly and steadfastly, to gain in acceptance. Meprobamate (Miltown) is prescribed by the medical profession more than any other tranquilizer in the world.

The reasons are not hard to find. Miltown is a *known* drug. Its few side effects have been fully reported. ***There are no surprises in store for either the patient or the physician.***

rs of clinical use...

Proven

in more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

- 1 simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
- 2 no cumulative effects, thus no need for difficult dosage readjustments
- 3 does not produce ataxia, change in appetite or libido
- 4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- 5 does not impair mental efficiency or normal behavior

Miltown®

meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; or as MEPROTABS®—400 mg. unmarked, coated tablets.

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 WALLACE LABORATORIES / Cranbury, N. J.

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while they are planning
their family

they need your help
more than ever



the most widely prescribed contraceptive

WHENEVER A DIAPHRAGM IS INDICATED

Against the "Vaginitis Spectrum"

TRICHOMONAS
MONILIA
BACTERIA

A welcome clinical advance...
effective medication
in an appealing form



Soft and pliant as a tampon, the Milibis vaginal suppository offers proved therapeutic action* in a vehicle giving unusual clinical advantages to both patients and physician.

COVERS CERVIX AND VAGINAL WALL—The pliant Milibis suppository disintegrates readily and molds itself to the cervix as well as the columns and rugae of the vaginal vault.

SHORT DOSAGE SCHEDULE—The short course of treatment with Milibis—only 10 suppositories in most cases—together with the clean, odorless, non-staining qualities eliminates psychic barriers which often interrupt longer treatments before complete cure.



SUPPLIED: BOXES OF 10
with applicator.

Now supplied with
plastic applicator
• SANITARY
• INSURES CORRECT
SUPPOSITORY PLACEMENT

MILIBIS® Vaginal Suppositories

Winthrop LABORATORIES
New York 18, N.Y.

*97 per cent effective in a study of 564 cases;
94 per cent effective in a series of 510 cases.

Milibis (brand of glycoharsol), trademark reg. U.S. Pat. Off.



the gentlest doctors in town
stop pain with **Nupercainal**[®]
(dibucaine CIBA)

...For minor cuts and burns, sunburn, hemorrhoids, removing sutures, performing routine office surgery, making instrument examinations. And, to best suit every situation, there's a choice of Ointment, Cream, Lotion, Suppositories.

2/2774MB

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in Gynecologic Bleeding

Control hemorrhage promptly & safely



with "PREMARIN" INTRAVENOUS

the physiologic hemostat

Rapid control of functional uterine bleeding with "Premarin" Intravenous is especially valuable in the ex-sanguinated patient and in young girls when curettage is not feasible.¹ "The acutely hemorrhaging patient can also be benefited by intravenously administered estrogen, no matter what the underlying cause, by preventing further shock and tiding the patient over...."²

Over 1,500,000 "Premarin" Intravenous injections have been given to date without a single report of

toxicity — to control spontaneous hemorrhage, and to minimize blood loss during and after surgery.

"Premarin"® Intravenous (conjugated estrogens, equine) package contains one "Secule"® providing 20 mg., and one 5 cc. vial sterile diluent. (Dosage may be administered intramuscularly to small children.)

1. Randall, L. M. 2. Reich, W. J., Rubenstein, M. W., Nechtow, M. J., and Reich, J. B. (literature available on request).

AYERST LABORATORIES
New York 16, N. Y. Montreal, Canada



diagnosis
without
delay



in hysterosalpingography
for detecting uterine
and tubal abnormalities

Ortho Pharmaceutical Corporation
RARITAN, NEW JERSEY



IN HEARTBURN OF PREGNANCY, PATIENTS SAY...
TASTY IS THE WORD FOR

titrалак®

UNIQUE ANTACID WITH MILK-LIKE ACTION

TABLETS
and
"teaspoon dose"
LIQUID

TITRALAC is being widely prescribed in heartburn of pregnancy, simple hyperacidity, and peptic ulcer because of these outstanding features:

- creamy, mint flavor...no chalky taste
- acts in seconds...lasts for hours
- non-constipating...no acid rebound

TITRALAC is effective in small doses. One teaspoonful TITRALAC Liquid approximates 2 tablets which contain 0.36 gm. glycine and 0.84 gm. calcium carbonate.

ACID NEUTRALIZING POWER

only 2 teaspoonfuls

or
2 tablets



ALSO WITH A SPASMODYLIC...

titrалак-sp

(Titralac formula + 0.5 mg. atropine methiodide)

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Manufacturers of MISTRAPEAK
for peptic ulcer reactions

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FROM CARNATION...a ready-prepared evaporated milk formula. Carnalac is simply Carnation Evaporated Milk with its added Vitamin D, plus carbohydrate. The carbohydrate is natural lactose from the milk, and added maltose-dextrin syrup. Mother adds water in the amount you recommend.

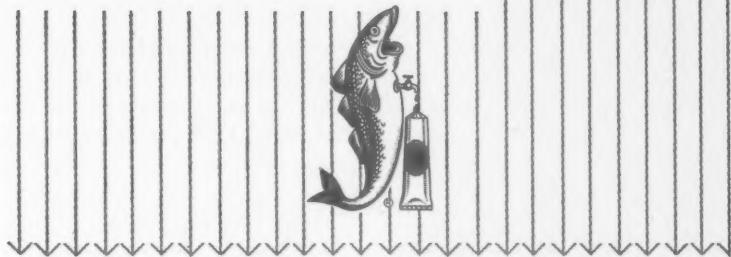


CARNATION EVAPORATED MILK IS THE WORLD'S
LEADER FOR INFANT FORMULA FEEDING

"from Contented Cows"



more than just vitamins A and D



DESITIN[®] ointment

also provides
unsaturated fatty acids as well as the vitamins A and D (of high grade Norwegian cod liver oil)—essential to skin health and integrity

and ingredients that are emollient, lubricant, gently astringent, protective, and aid tissue repair (zinc oxide, talcum, petrolatum and lanolin)

in a smooth creamy ointment so processed that one application of Desitin soothes, protects, and promotes healing for hours in...

diaper rash
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(decubitus, diabetic, varicose)
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Samples Please write... **DESITIN CHEMICAL COMPANY**
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CONSISTENTLY GOOD
CLINICAL RESULTS
IN TRICHOMONAL
AND MONILIAL VAGINITIS

TRICOFURON IMPROVED (Suppositories and Powder)
cured 143 of 161 patients with vaginitis due to
Trichomonas vaginalis, Candida (Monilia) albicans,
or both. "Almost immediate symptomatic
improvement was noted with the first insufflation."

Criteria for cure: freedom from
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This cure rate of 88.8% is "surprisingly similar"
to results reported by earlier investigators.

Coolidge, C. W.; Glisson, C. S., and Smith, A. S.:
J.M.A. Georgia 48:167, 1959.

TRICOFURON®
IMPROVED

2-step treatment brings swift relief,
eradicates stubborn trichomonads,
Candida (Monilia) albicans,
Hemophilus vaginalis

1. POWDER for weekly insufflation in your office.
MICOFUR®, brand of nifuroxime, 0.5%
and FUROXONE®, brand of furazolidone, 0.1% in
an acidic water-dispersible base.

2. SUPPOSITORIES for continued home use
—1st week one suppository in the morning
and one on retiring. After 1st week, one
suppository at night may suffice.

Continue use of suppositories during menses.
Treatment should be continued throughout a complete
menstrual cycle and for several days thereafter.

MICOFUR 0.375% and FUROXONE 0.25%
in a water-miscible base.

*Rx new box of 24 suppositories with applicator
for more practical and economical therapy.*

*Also available:
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NITROFURANS—a unique class of antimicrobials
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MIDNIGHT SNACKS for ICE-BOX RAIDERS		U ₂ medium	Calories	Protein Gm.
	Weight			
Cold potato.....	65		1.5	
Chicken leg.....	88		15.0	
Milk.....	140		7.0	
Mouthful of roast.....	130		11.0	
Piece of cheese.....	120		7.2	
Left-over beans.....	95		6.6	
Brownie.....	90		3.9	
Cream-puff.....	70		5.7	
 SWEETS				
Ice cream.....	100			
Plain vanilla.....	100		4.0	
Chocolate and other.....	100		4.5	
Milk sherbet.....	100		4.0	
Sundaes, small chocolate.....	100		10.0	
Ice cream sodas, chocolate.....	100		3.5	
 CANDIES				
Chocolate bars, 5c size.....	90			
Plain.....	90		2.0	
With nuts.....	95		5.0	
Chocolate covered bar.....	100		5.0	
Chocolate cream, bonbon.....	100		0.6	
Caramels.....	15			
Plain.....	15		0.5	
Chocolate nut caramel.....	60		0.8	
 DESSERTS				
Pie.....				
Fruit—apple, etc.....	560		5.5	
Custard.....	360		8.5	
Lemon meringue.....	470		5.0	
Pumpkin pie with whipped cream.....	460		9.0	

ESKATROL®

brand of dextro amphetamine and prochlorperazine

SPANSULE®

brand of sustained release capsules

is particularly useful in
overweight patients who
have exhibited *nervousness*
and *insomnia* on previous
reducing regimens.



During more than a year's clinical testing, 'Eskatrol' demonstrated a remarkably low incidence of side effects—particularly nervousness and insomnia. In a typical series of more than 200 overweight patients on restricted diets, nervousness—the most frequent complaint with other anti-appetite preparations—troubled only 5%. Only 4.6% experienced insomnia—an incidence close to placebo level.

Formula: Each 'Eskatrol' Spansule capsule contains 15 mg. of Dexedrine® (brand of dextro amphetamine sulfate) and 7.5 mg. of Compazine® (brand of prochlorperazine, as the dimaleate).

Dosage: One capsule in the morning.

R size: Bottles of 30 capsules.

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extends the usefulness of Vitamin K₁ therapy[†]

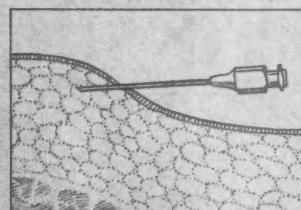
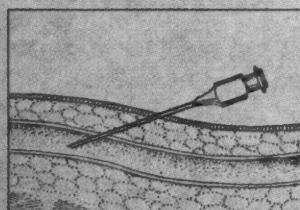
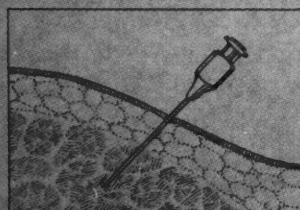
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AQUEOUS COLLOIDAL SOLUTION

[†]a clear, stable, aqueous colloidal solution for administration

- intramuscularly
- intravenously
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a dosage form for every Vitamin K indication:

AquaMEPHYTON (for intramuscular, intravenous, subcutaneous administration), 1-cc. ampuls containing 10 mg. MEPHYTON, Vitamin K,

TABLETS MEPHYTON (for oral administration), 5 mg.

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1-cc. ampuls containing 10 mg. and 50 mg. per cc.

MEPHYTON®

OF MEPHYTON®, VITAMIN K₁

*Vitamin K₁ "has a more prompt, more potent and more prolonged effect than the vitamin K analogues" **

*Council on Drugs: New and Nonofficial Drugs,
Philadelphia, J. B. Lippincott Co., 1960, p. 732

reduces the hazard of hemorrhage
due to hypoprothrombinemia in:

- prophylaxis and therapy of hemorrhagic disease of the newborn
- surgery, preoperatively and postoperatively
- anticoagulant-induced prothrombin deficiency
- inadequate absorption of Vitamin K
- biliary tract disease
- prothrombin-depressing drugs such as salicylates and phenylbutazone
- inadequate endogenous production of Vitamin K

For additional information, write Professional Services,
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MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., WEST POINT, PA.

AquaMEPHYTON AND MEPHYTON ARE TRADEMARKS OF MERCK & CO., INC.



Rapid and effective relief of pruritus vulvae...regardless of cause

HIST-A-CORT-E renders unquestionable relief of pruritus vulvae associated with either specific or non-specific afflictions of the female external genitalia.¹ HIST-A-CORT-E, a well-balanced combination of proven ingredients, not only controls inflammation, edema and pruritus . . . but facilitates healing and restores the normal tonicity and vitality of the mucosa and skin.

1. Greenblatt, R. B., Manautou, J. M., Griffin, T. L. and Henry, J. W.: Geriatrics 13:235-238, (April) 1958.

HIST-A-CORT-E® CREME (pH 4.7) LOTION

micronized hydrocortisone alcohol, vitamin A, estrone, pyrilamine maleate in the exclusive ACID MANTLE® vehicle.

DOME CHEMICALS INC.
New York — Los Angeles

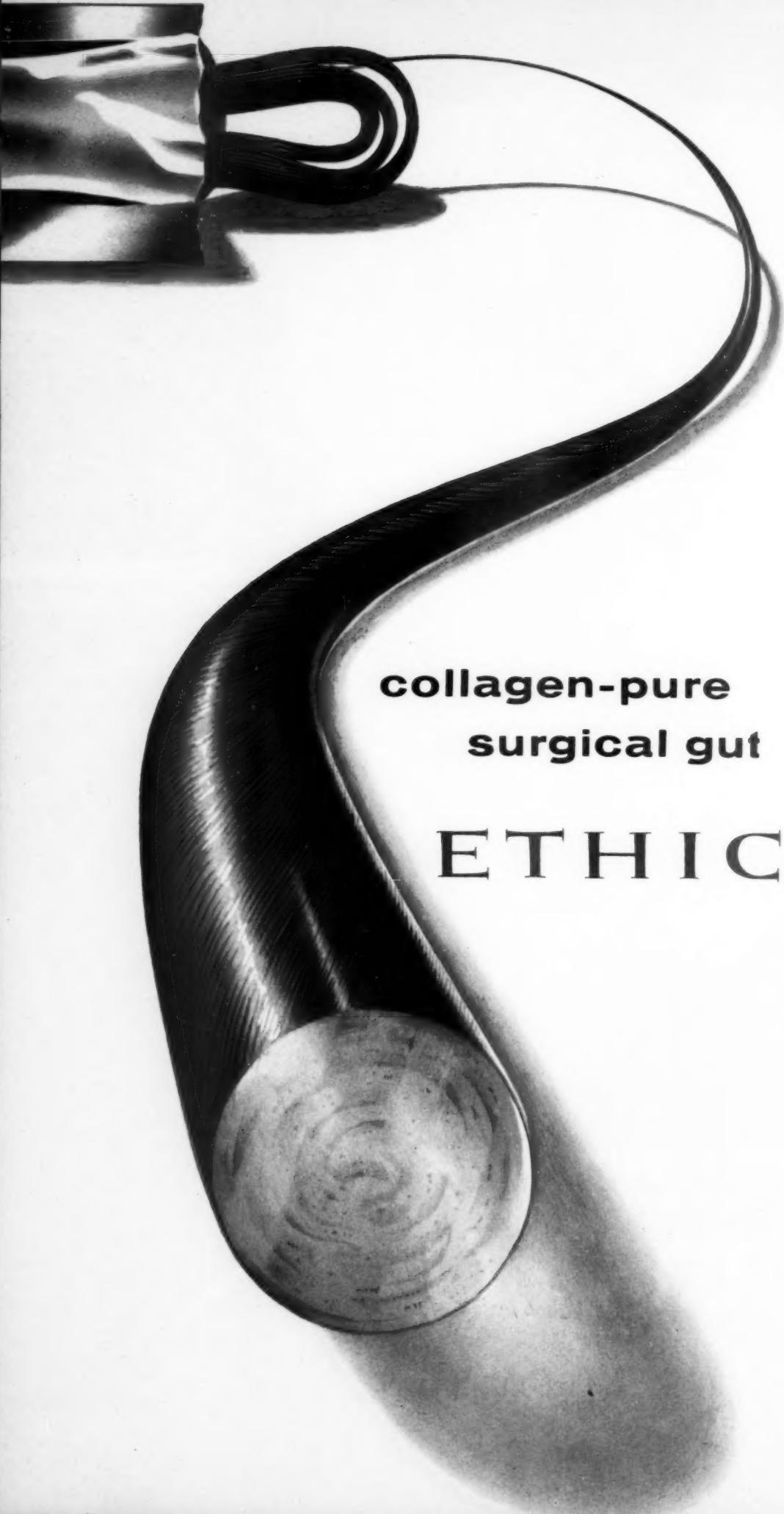




advancing with surgery

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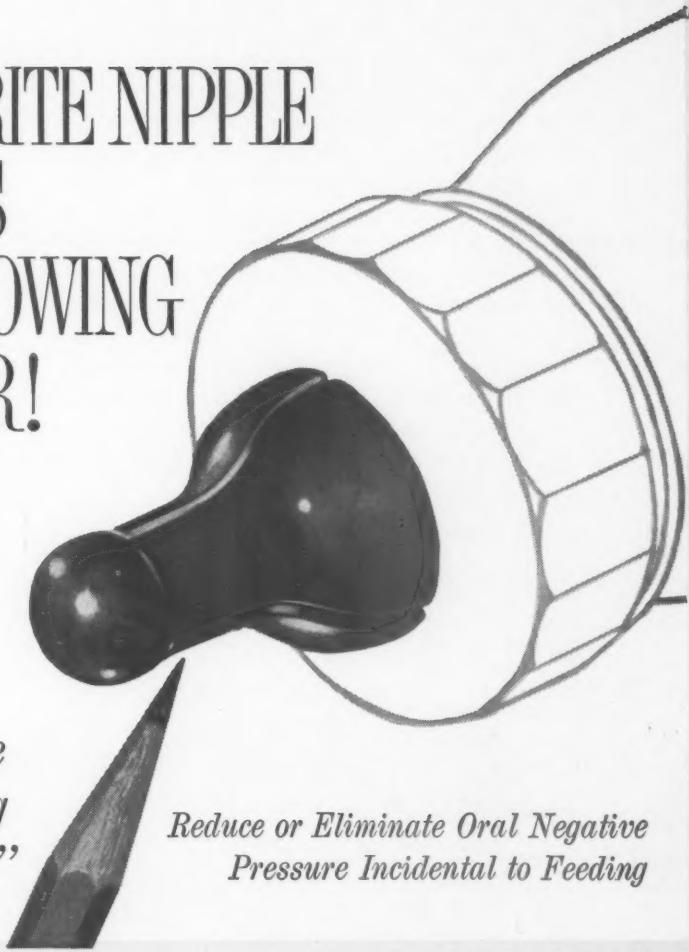




**collagen-pure
surgical gut**

ETHICON®

NEW FEED-RITE NIPPLE MAKES SWALLOWING EASIER!



*Exclusive
"Breathing
Channels"*

*Reduce or Eliminate Oral Negative
Pressure Incidental to Feeding*

The new Feed-Rite Nipple eliminates the problem of oral vacuum build-up. *Three "breathing channels"* enable the infant to *breathe as he feeds*, making possible a natural, *uninterrupted* swallowing action. Aerophagia is reduced... less bubbling is required.



The nipple, with its extra soft tip and base, adjusts to pressure changes which regulate the flow to a pace most comfortable for the infant. Special air vent helps keep formula flow constant... reduces nipple collapse.

FEED-RITE NIPPLE NOW FEATURED ON ALL DAVOL NURSERS:

- FEED-RITE PLASTIC
- FEED-RITE DURAGLAS
- NEW ECONOMY FEED-RITE:
"Twin Dimple" finger grips provide more secure handling. Economically priced along with other popular nursers.



RUBBER COMPANY
PROVIDENCE 2, R.I.

THE CLINICAL STUDY¹: Treatment of obesity.

THE PATIENTS: 73 patients—26 obstetrical,
47 non-obstetrical—all of whom
had previously dieted unsuccessfully.

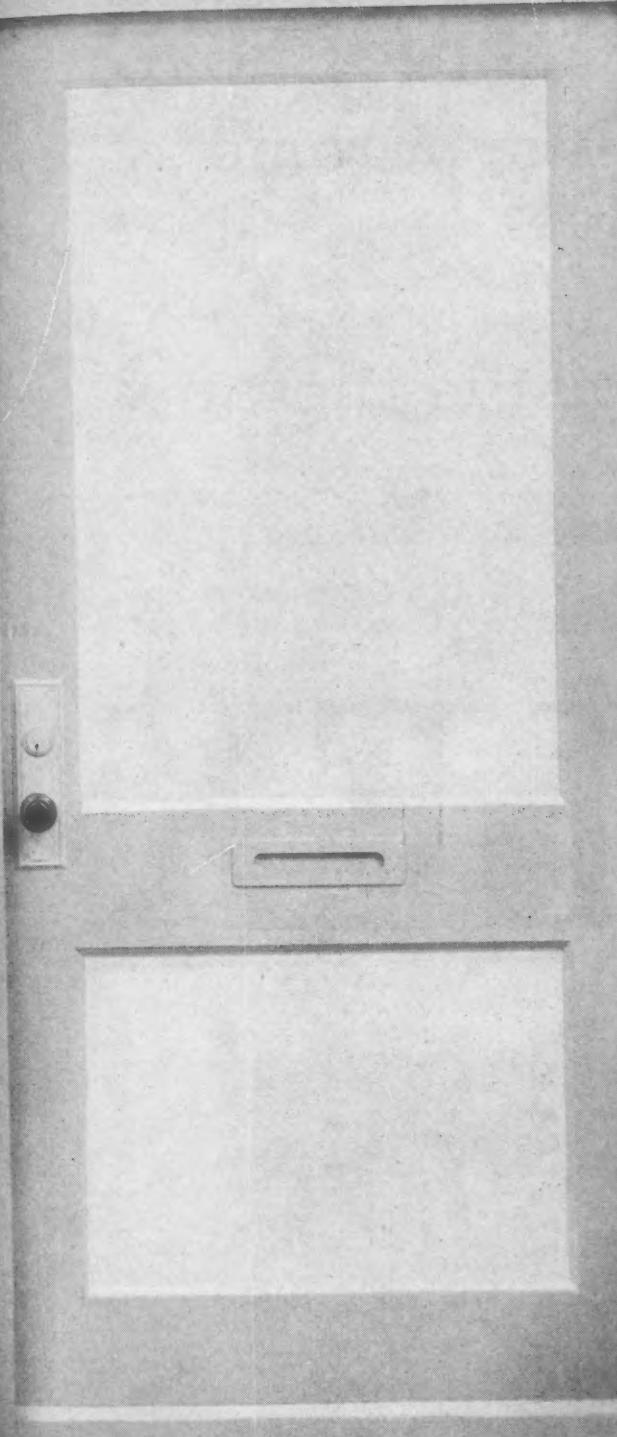
THE DOSAGE: 5, 10 or 15 mg., orally,
once daily, in the morning.

THE RESULTS: Average weight loss of 20.8 lbs.
in non-obstetrical patients
treated from 5½ to 30 weeks;
average loss of 23.6 lbs. in
obstetrical patients (postpartum)
treated from 8 to 42 weeks.
All patients lost weight.

THE RECORD: Rate of drug absorption seemed to
allow a very smooth effect. Mood
elevation and appetite depression
were gradual and continuous. In
only 5 patients (all obstetrical)
did side effects indicate corrective
dosage reductions.

¹Sherman, A. I., St. Louis, Mo.; Communication to
Medical Department, Abbott Laboratories,
Oct. 6, 1959.





THE DRUG:

DESOXYN® Gradumet®

(Methamphetamine Hydrochloride in Long-Release Dose Form,* Abbott)

All-day appetite control from a
single oral dose—5, 10 or 15 mg.



for the silent syndrome*...

*the unmentioned edema, mood changes,
GI distress, preceding menstruation

a comprehensive therapy

NEW



to relieve the symptoms of

for EDEMA...

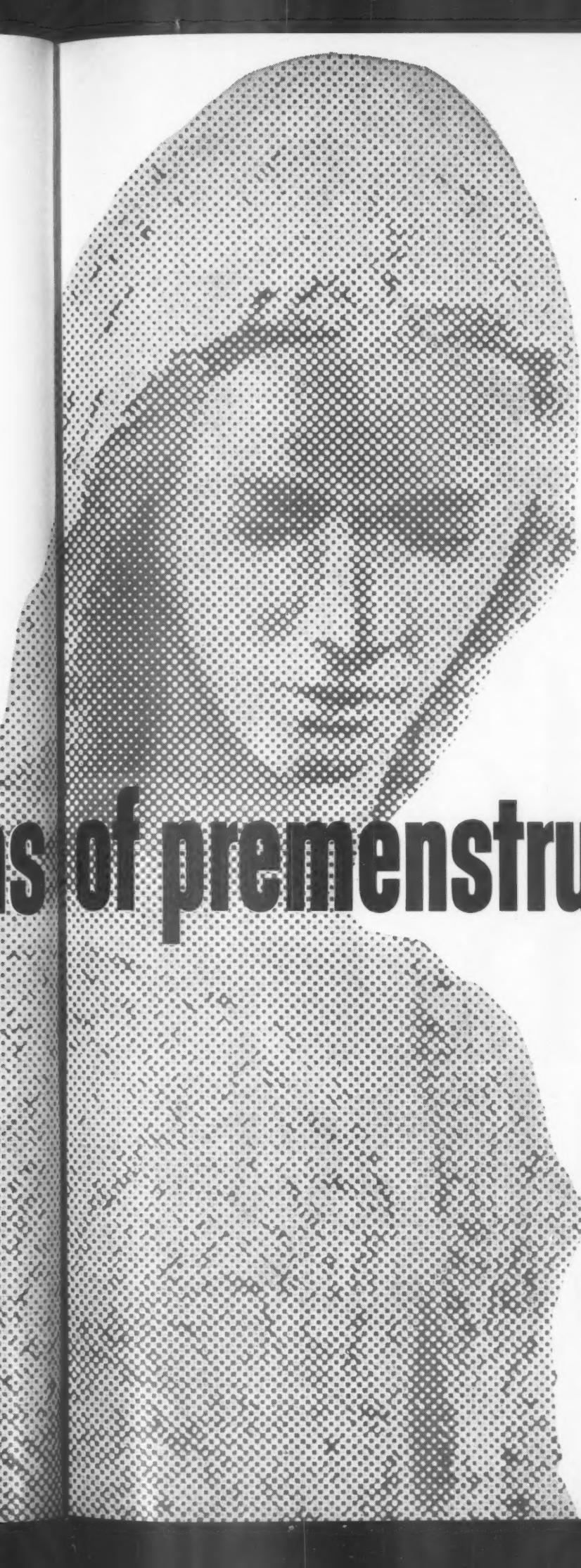
CYCLEX provides the prompt
diuresis of HYDRODIURIL
for rapid reduction of
weight gain, breast fullness,
abdominal congestion

for MOOD-CHANGES...

CYCLEX supplies the effective
relief of meprobamate for nerv-
ousness, irritability, tension,
nausea, malaise, insomnia

for GI DISTRESS...

CYCLEX affords quick-acting
relief of nausea and
bloating associated with
premenstrual tension.



INDICATION: CYCLEX is indicated for the relief of premenstrual tension with edema.

USUAL DOSAGE:

One CYCLEX Tablet 1 or 2 times daily, beginning when symptoms appear and continuing until the onset of menses.

S of premenstrual tension

SUPPLIED: CYCLEX Tablets are supplied in bottles of 100. Each tablet contains 25 mg. of hydrochlorothiazide and 200 mg. of meprobamate.

Additional information on CYCLEX is available to physicians on request.

CYCLEX and HYDRODIURIL are trademarks of Merck & Co., Inc.



MERCK SHARP & DOHME
Division of Merck & Co., Inc.
West Point, Pa.

**safe
and
sound**
in any pregnancy

to prevent morning sickness

With new Tigan 250 mg capsules you can now provide protection against morning sickness with only two capsules daily—at bedtime and in the morning. Tigan is so safe that it may be used with confidence as a routine prescription in any pregnancy. Avoiding the risks of phenothiazine derivatives and the limitations of the antihistamines, Tigan acts both therapeutically and prophylactically to stop active vomiting or to prevent nausea and vomiting.

Consult literature and dosage information, available on request, before prescribing.

Tigan Bibliography: 1. M. W. Goldberg, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 2. O. C. Brandman, *ibid.* 3. J. A. Lucinian and R. H. Bohn, *ibid.* 4. D. W. Molander, *ibid.* 5. B. I. Shnider and G. L. Gold, *ibid.* 6. W. S. Derrick, *ibid.* 7. B. Wolfson and F. F. Foldes, *ibid.* 8. L. McLaughlin, *ibid.* 9. W. K. Gauthier, Discussant, *ibid.* 10. H. E. Davis, Discussant, *ibid.* 11. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, 9:189, 1958. 12. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, 126:270, 1959. 13. W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, *New York J. Med.*, 59:4217, 1959. 14. O. W. Doyle, *Clin. Med.*, 7:43, 1960. 15. L. A. Nathan, *Curr. Therap. Res.*, 2:6, 1960. 16. Council on Drugs, New and Nonofficial Drugs, *J.A.M.A.*, 172:1038, 1960. 17. O. L. Davidson, *J. Tennessee M. A.*, 53:140, 1960. 18. O. Brandman, *Gastroenterology*, 38:777, 1960. 19. B. A. Robin, *Maryland M. J.*, to be published. 20. A. L. Kolodny, *Am. J. M. Sc.*, 239:682, 1960. 21. F. Cacace, *Colorado GP*, 2:5, 1960.

TIGAN® Hydrochloride—4-(2-dimethylaminoethoxy)-
N-(3,4,5-trimethoxybenzoyl)benzylamine hydrochloride



Division of Hoffmann-La Roche Inc.

Tigan

NEW 250 mg

CAPSULES

for faster, more prolonged, more effective antiemetic activity

for laxative results without laxative harshness

in **DOXIDAN®** THE SURFACTANT LAXATIVE
obstetrics

"We consider Doxidan to be superior to the agents we have previously employed in the treatment of constipation in postpartum patients. Not only was it more effective, but also its use was associated with almost complete freedom from side effects . . . flatulence, cramping and 'griping' were notably absent . . . 'rebound constipation' and the danger of subsequent habit formation are largely obviated by the use of this logical combination of a potent fecal softener with a mild peristaltic stimulant."¹

DOSAGE AND SUPPLY: One or two capsules administered at bedtime for two or three days or until bowel movements are normal. Each maroon Doxidan capsule contains 50 mg. Danthron (1,8-dihydroxyanthraquinone) and 60 mg. calcium bis-(dioctyl sulfosuccinate). Bottles of 30 and 100 soft gelatin capsules.

¹. Boil, A.: Management of Constipation in the Puerperium. Accepted N. Y. S. J. Med.



LLOYD BROTHERS, INC.
CINCINNATI 3, OHIO, U.S.A.



BUFFERED TO MAINTAIN A NORMAL, LOW pH...LOW SURFACE TENSION
FOR THOROUGH CLEANSING OF THE VAGINAL MUCOSA...

Buffers in Massengill Powder solution (pH 3.5 - 4.5) inhibit the neutralizing effect of an alkaline mucosa, maintaining a healthy, low pH for 4 to 6 hours in ambulant patients and up to 24 hours in recumbent patients. This low pH represses the propagation of candida, trichomonas vaginalis, and pathogenic bacteria but permits growth of the beneficial Döderlein bacillus. In contrast, an ordinary, unbuffered douche like vinegar is neutralized within 30 minutes after application. • Low surface tension of Massengill Powder solution (50 dynes/cm.) enables it to penetrate and cleanse all the folds of the vaginal mucosa more effectively than vinegar (surface tension of 72 dynes/cm.). It also makes cell walls of infecting organisms more susceptible to therapy.

MASSENGILL[®] POWDER

the buffered acid vaginal douche with low surface tension

THE S. E. MASSENGILL COMPANY Bristol, Tennessee • New York • Kansas City • San Francisco



PATIENTS PREFER

MASSENGILL[®] POWDER

the buffered acid vaginal douche with low surface tension

Massengill Powder soothes inflamed tissues, deodorizes, and tends to diminish excessive vaginal secretions. Patients like its clean, refreshing odor.

Massengill Powder is indicated for routine feminine hygiene to guard against infection, and as an adjunct in the management of candida, trichomonas, staphylococcus, and streptococcus vaginal infections.

Contains: Ammonium Alum, Boric Acid, Phenol, Menthol, Berberine, Thymol, Eucalyptol, and Methyl Salicylate. Write for samples and detailed literature.

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For more successful pregnancies in habitual aborters

When added to your individualized anti-abortive regimen, NUGESTORAL may help you bring more habitual aborters to successful term.

By supplying five therapeutic agents known to contribute to fetal salvage, NUGESTORAL creates an optimal maternal environment for the maintenance of pregnancy.

Nugestoral supplies in each daily dose of three tablets:

Progesterol® (Ethisterone)	45.0 mg.
• Progestational action helps maintain fetus	
• Relieves uterine spasticity	
Ascorbic Acid (Vitamin C)	525.0 mg.
Purified Hesperidin	487.5 mg.
(equiv. 600 mg. hesperidin complex)	
• Prevent or correct abnormal capillary fragility	
• Protect and strengthen decidual vessels	
Menadione Sodium Bisulfite	6.0 mg.
(U.S.P. Equivalency)	
• Prevents hypoprothrombinemia in mother and child	
dL, Alpha-Tocopherol Acetate (Vitamin E)	10.5 mg.
• Extra nutritional insurance	

DOSAGE: Prophylactic — One NUGESTORAL tablet t.i.d. from diagnosis through at least the second trimester.

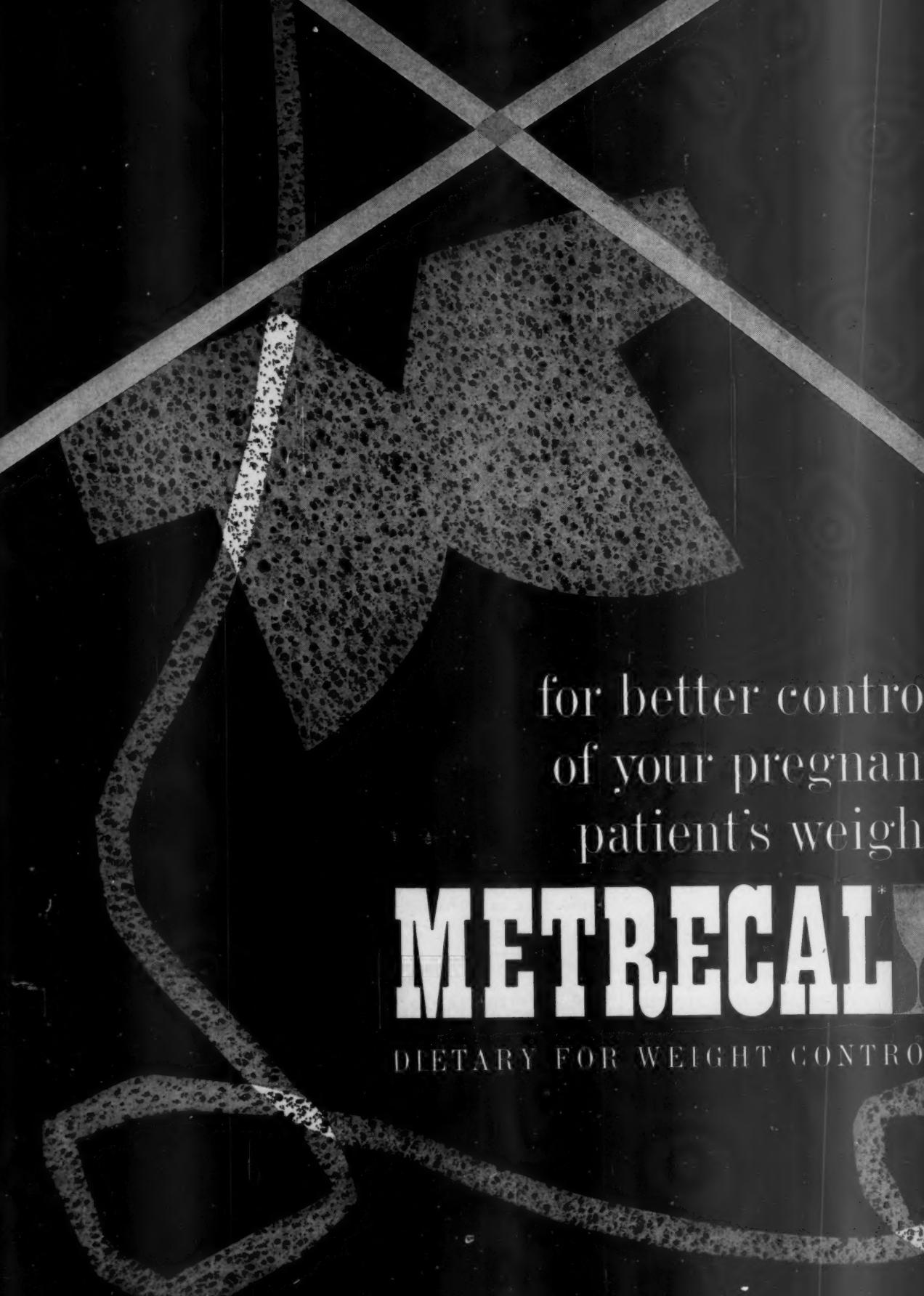
Symptomatic — Two tablets t.i.d. or q.i.d. until symptoms are controlled. Then one tablet t.i.d.

Available in boxes of 30 and 100. Write for copies of recent clinical reports.



ORGANON INC., ORANGE, N. J.

Nugestoral®



for better control
of your pregnant
patient's weight

METRECAL*

DIETARY FOR WEIGHT CONTROL



measured calories to help keep your patients at optimal weight levels...without appetite depressants

sound nutrition with limited calories during pregnancy

Metrecal may be used as the cornerstone around which to build a pregnancy diet when you wish to keep your patient's weight from rising too rapidly and to effect weight loss when necessary. A half-pound of Metrecal mixed with a quart of water supplies 900 calories in pleasant-tasting beverage form. This quantity provides 70 Gm. of protein, plus all essential vitamins and minerals. It is rich in calcium (2.0 Gm.) and iron (15 mg.). This daily ration may be divided into four glasses—one for each meal—and one at bedtime.

highly flexible

When substantial weight loss is indicated in pregnancy, Metrecal alone can provide the 900-calorie diet. Metrecal can also be used for one or two meals a day, as the total diet two or three days a week, or it may be used at meals with other foods. In the postpartum period, Metrecal provides an excellent method for losing weight or preventing additional weight gain.

gratifying patient cooperation

The high satiety, simplicity of use and palatability of Metrecal provide patients with a strong motivation to cooperate in weight-control programs.^{1,2} Metrecal can provide a more dependable and nutritionally sound diet than the complex dietary schedules frequently used.

no appetite depressants required

Metrecal relies on sound nutritional principles for weight control rather than appetite depressants or diet "aids." Its pleasant taste and high satiety will help control the patient's appetite.

easy to use—easy to prepare—variety of flavors

All your patients do is mix Metrecal and water to a creamy, palatable smoothness with a blender, eggbeater or fork, refrigerate and serve. For variety in the diet, Metrecal is available in plain, chocolate and butterscotch flavors.

Metrecal Weight-Control Guide is available from your Mead Johnson Representative or by writing to us, Evansville 21, Indiana.

References: (1) Antos, R. J.: Southwestern Med., 40:695-697 (Nov.) 1959. (2) Tullis, L. E. to be published.



Mead Johnson
Symbol of service in medicine

T.M.

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**PREVENT
RE-INFECTION
IN VAGINAL
TRICHOMONIASIS**

**THE HUSBAND
A
PRIMARY
SOURCE OF
RE-INFECTION**

The role of the husband as a carrier and as a cause of re-infection in vaginal trichomoniasis is well documented.¹⁻⁷

"Until and unless immunization is possible, definite prophylactic measures such as the use of condoms, at least during the course of therapy in the female, have the same importance in the eradication of this disease as the elimination of endogenous extravaginal foci of infections."⁸

ENLIST HIS COOPERATION—SPECIFY RAMSES®
the prophylactic with "built-in" sensitivity

Husbands readily cooperate when you recommend RAMSES prophylactics. The exquisite sensibility preserved by this tissue-thin, natural gum-rubber sheath of amazing strength and solid clinical reliability places RAMSES almost out of human awareness. Without imposition or deprivation for the sake of cure, the routine use of RAMSES with "built-in" sensitivity is readily adopted—even by the husband whose fear of sensation loss is a consideration.



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References: 1. Baum, H. C.: M. Clin. North America 42:263 (Jan.) 1958. 2. Decker, A.: New York J. Med. 57:2237 (July 1) 1957. 3. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. 76:666 (Sept.) 1958. 4. Karnaky, K. J.: South. M. J. 51:925 (July) 1958. 5. Maeder, E. C.: Journal-Lancet 79:364 (Aug.) 1959. 6. McDonald, J. H.: M. Clin. North America 42:267 (Jan.) 1958. 7. Riba, L. W.: Am. J. Obst. & Gynec. 73:174 (Jan.) 1957.

JULIUS SCHMID, INC. 423 West 55th Street, New York 19, N. Y.



off to a good day—constipation relieved

Pleasant-tasting Agoral is the laxative virtually tailor-made for busy people. Taken at bedtime, Agoral works effectively and gently overnight, without disturbing sleep, to produce a normal bowel movement the next morning—*before* the day's activities begin.

agoral®

the gentle laxative

AG-N803





MORNIDINE®

(brand of pipamazine)

for suppression of
morning sickness

Vallestril®

*"...relief of [menopausal] symptoms
was observed⁵ in 91 per cent of the
patients treated with methallenestril
[Vallestril]...."*



Research Briefs from Searle

Mornidine was found clinically effective in morning sickness in more than 90 per cent of the women treated. "Experimental work and clinical observations¹ to date indicate that this phenothiazine is . . . an effective antiemetic with exceedingly low toxicity. . . ."

The effect of Enovid in patients with endometriosis has been described² as follows: "Enovid is a potent, orally effective progestin. The addition of 3-methyl ether of ethynodiol prevents 'breakthrough' bleeding and produces an ideal mimic of the hormonal changes of pregnancy. Enovid inhibits ovulation, induces a secretory endometrium and produces a decidual effect in areas of endometriosis. It is postulated that, after five to six months of such treatment, decidual necrosis occurs and is followed by gradual absorption."

"The first principle [in the treatment of trichomonas vaginalis] is that of restoring the pH of the vagina to the usual degree of acidity (3.5 to 4.5), at which the normal flora of the vagina may eradicate the trichomonad. . . . We have found³ Floraquin (diiodohydroxyquinoxine [compound]), 2 tablets nightly, to be acceptable. . . ."

Valestril has proved⁴ to be appropriate in controlling the menopausal syndrome without adverse side effects in dosage of 3 mg. per day.

References:

1. Friend, D. G.: Current Drug Therapy: The Phenothiazines; Clin. Pharm. & Therap. 1:5 (Jan.) 1960.
2. Kistner, R. W.: Endometriosis and Infertility, Clin. Obst. & Gynec. 2:877 (Sept.) 1959.
3. Wilson, L. A., Trichomonas Vaginalis Vaginitis, in Conn, H. F.: Current Therapy—1960, Philadelphia, W. B. Saunders Company, 1960, p. 657.
4. Kupperman, H. S.: The Choice of Drugs in Endocrine Dysfunction, in Model, W.: Drugs of Choice 1960-1961, St. Louis, The C. V. Mosby Company, 1960, p. 584.
5. Goldfarb, A. F., and Napp, E. E.: Use of Methallenestril (Valestril) in Control of Menopausal Symptoms, J.A.M.A. 161:616 (June 16) 1956.



Nonsurgical treatment of
Endometriosis with
ENOVID®

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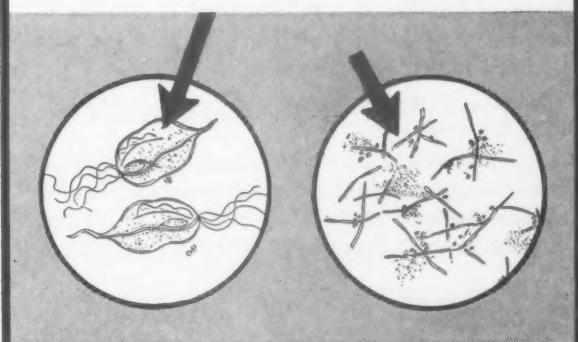
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*Berberian, D. A., and Slichter, R. G.: J.A.M.A. 168:2257 (Dec. 27) 1958.

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OBSTETRICS

Technique for the *in situ* study of placental transport in the pregnant guinea pig

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THE importance of the placenta for growth and development of the fetus has been realized for many years but because of technical difficulties the exact role of the placenta in the transport of substances between mother and fetus is not well understood. Most *in vivo* studies of placental transport have utilized a technique of injecting a compound into the mother and measuring the concentration in the fetus, or the reverse of this procedure. In both cases evaluation

of such data is a complex problem, especially when rapidly metabolized substances are being studied.

In 1955, Alexander and associates¹ reported a study of placental transport in sheep, using a technique where the fetus was removed by hysterotomy and the umbilical vessels perfused. With this method they were able to obtain direct information that could only be inferred by previous investigators. Although this technique had much to offer over other methods, it seemed to us more desirable to study the placenta in a readily accessible and inexpensive animal, preferably one with a placenta similar to the human. The guinea pig filled some of these criteria but the small size of the placenta and associated vessels presented many technical problems. The solution of each proved relatively simple but they had to be solved in turn before it was possible to successfully develop and use the tech-

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Fig. 1. The relationship of the various parts of the apparatus set up for a placental perfusion.

nique. After approximately 3 years' effort the technical problems have been solved and it is now possible to apply the technique with success and regularity. The present report describes the technique in detail and following papers will present information derived from its application.

Experimental animals

Pregnant guinea pigs dated at the time of mating were obtained from commercial breeders. The animals were delivered to the laboratory usually between 40 and 50 days of gestation and were maintained in animal rooms until used. Some experiments have been done as early as the forty-fifth day but most animals were used after 50 days of pregnancy.

Description of the apparatus

The complete relationship of the various parts set up for an actual open system perfusion study is shown in Fig. 1. For the sake of clarity the component parts (with-

out the large water bath) and circulation pump may be seen in Fig. 2. In setting up the apparatus, the following procedure is used:

1. A large stainless steel tank, 21 by 13 by 7 inches (Fig. 1), the sides of which are covered with asbestos, is used to maintain a constant temperature.

2. An inner tray (Fig. 2, A), measuring 13 by 9 $\frac{3}{4}$ by 2 $\frac{1}{2}$ inches, made of thin stainless steel, is placed at one end of the water bath and held in place by screws or clamps.

3. The outer water bath is filled with tap water (40 to 43° C.). For experiments of 45 to 60 minutes' duration this temperature is sufficient to maintain the inner tray at 36 to 38° C. If conditions so require, heating elements and thermostatic controls may be used in the water bath. For most short experiments, this has not proved necessary.

4. A pregnant guinea pig previously given 0.2 c.c. of Nembutal (intraperitoneally) is shaved along the left side of the abdomen.

The animal is then given ether and maintained in an anesthetized state for the duration of the study. In order to immobilize the animal completely throughout the experiment, it was found necessary to confine it in a frame (Fig. 2, B). This frame was made from ordinary galvanized $\frac{1}{2}$ inch screen, shaped into a "U." In the side of the screen a $2\frac{1}{2}$ by $3\frac{3}{4}$ inch hole was cut and the rough edges covered with adhesive tape. The frame was attached by ordinary copper wire through holes to an aluminum "T" constructed from $\frac{1}{8}$ inch aluminum. The "T" is 16 inches high; the crossbar is 8 by $2\frac{3}{4}$, and the upright is $3\frac{1}{4}$ inches wide. Holes ($\frac{1}{8}$ inch diameter) were drilled along the sides through which strings were inserted for tying down the animal's legs. The animal's head can be immobilized by means of another tie made through holes just below the crossbar of the "T." Threaded holes were made in the cross part of the "T" in order to insert screw clamps into place for holding syringes. These clamps were made by attaching ordinary battery clamps to the heads of brass bolts. The animal is tied in place and the wire screen securely tied around the body as may be seen in Fig. 1. This effectively prevents movement of the mother and possible destruction of the final setup.

5. The guinea pig attached to the "T" is then placed in position in the inner tray

(Fig. 1) and the latter filled with isotonic saline. A small platform made of thin aluminum (Fig. 2, C) is placed alongside the animal. The purpose of this platform is to keep the fetus and placenta in position throughout the remaining experiment. Through the hole in the wire screen, an incision 2 to 3 inches long is next made along the abdominal wall and the pregnant uterine horn removed into the saline bath. Once the uterine horn is removed from the cavity, the intestine tends to push out through the same opening. This is prevented by pushing several 4 by 4 inch gauze pads through the incision into the abdominal cavity and placing over the opening a thin aluminum shield (Fig. 2, D). The bottom part of this shield fits inside the open edge of the hole in the wire mesh screen. The shield is hooked either to the tray or to a bolt located on the opposite side of the animal. An incision is made in the uterus, and the fetus, umbilical cord, and placenta pulled in view. These are kept covered by saline at all times in the bath.

6. Although dissection of the umbilical vessels can be accomplished with the naked eye, magnification of the working area simplifies the procedure. For this we have found a Dazor lamp combining a floating magnifier and fluorescent lighting invaluable. Gauze pads are placed under the umbilical

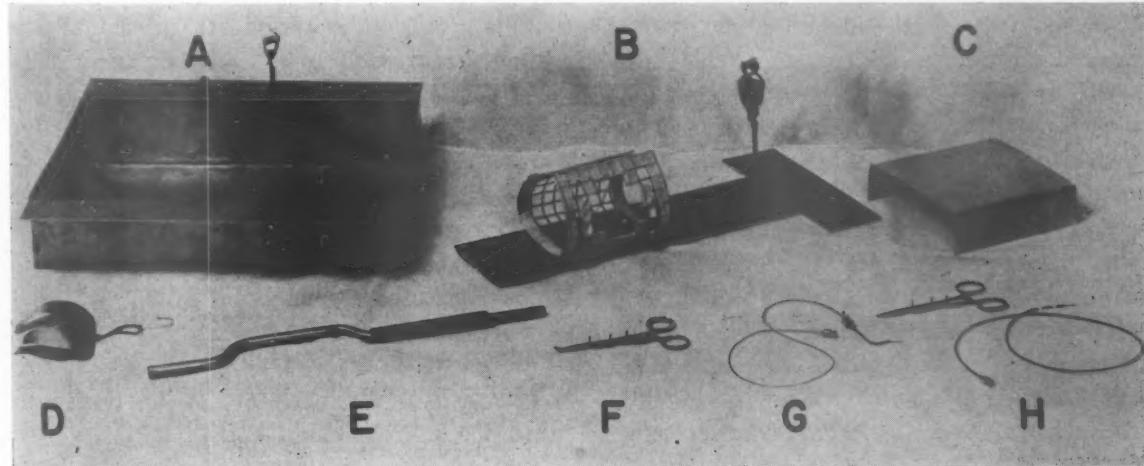


Fig. 2. The component parts of the placental perfusion apparatus. For description and use, see text.

cord and the surrounding connective tissue removed by means of fine-pointed jewelers' tweezers (Dumont No. 4). This is one of the most important steps of the whole technique. It is, however, one of the most critical. Extreme care has to be exercised to prevent rupture of the umbilical vein or collapse of the arteries. Excess pressure or cooling of the arteries may result in their immediate collapse.

7. One end of a $\frac{3}{8}$ inch brass rod constructed as shown in Fig. 2, *E* is placed in a clamp on the far side of the tray. This clamp is attached loosely so that a swivel action allows movement around it. The rod is attached to the near side of the tray by means of a large ball of modeling clay. A second mass of clay is attached to the rod adjacent to the first. This latter clay proved a simple but highly effective way of maintaining the needles and instruments in position during perfusion. Since the spacial relationship of the umbilical vessels, placenta, and fetus varies between animals, it has not been possible to utilize a constant fixed position for the needles. The clay makes possible wide latitudes of motion and position and solves this problem.

8. In order to eliminate fetal circulation during perfusion studies the umbilical cord is clamped off at the fetus by means of a hemostat, along one side of which several pins have been welded (Fig. 2, *F*). These pins can be inserted in the clay and effectively hold the fetal end of the cord in the desired position.

9. Once the cord has been clamped off, it is necessary to work fairly rapidly before the arteries collapse. The next step—and perhaps the most difficult—is inserting the needle into one of the umbilical arteries. The needle is made by cutting the shaft from a No. 23 hypodermic needle. The blunt end is inserted into a No. PE 20 polyethylene tubing (inside diameter, 0.015 inch; outside diameter 0.043 inch) threaded through a curved No. 16 hypodermic needle. Pulling the tubing into this "needle holder" forces a tight fit and the whole unit becomes fairly rigid. Two pins (for holding the

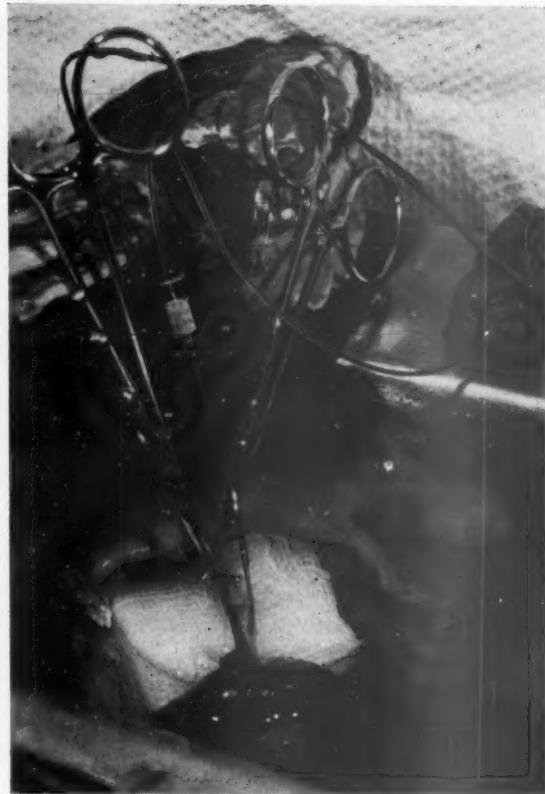


Fig. 3. The positioning of needles in place for perfusion. For photographic purposes the umbilical vessels have been separated and saline removed.

needle into the clay) are soldered to the side of the needle head (Fig. 2, *G*).

10. With one hand it is possible to slip the needle into the artery while the other hand presses the pins firmly into the clay. Although this is a delicate procedure the artery is capable of a surprising amount of manipulation. The needle is inserted as far as possible into the artery and at the same time the point of entry raised slightly above the surface of the saline. This results in about half of the needle being below saline level. We have found that the portion of the artery not covered by saline will constrict down onto the needle. Thus, since the needle is firmly held by the constricted artery, it is not necessary to tie the vessel in place. No amount of pressure exerted through the arterial tubing will, under these conditions, force the needle out of the artery. If, however, the whole needle and

enveloping artery are entirely covered by saline, the needle may slip from the relaxed artery. The presence of the needle within the artery can be checked by running a small amount of saline through the tubing.

11. It has been found that cannulation of the umbilical vein is most easily accomplished by holding the venous needle (Fig. 2, H) in a hemostat. The needle can be easily inserted into the vein and held in place by the clay (Fig. 3). The venous needle is made from the shaft of a No. 20 hypodermic needle and inserted into a No. PE 90 polyethylene tubing (inside diameter, 0.034 inch; outside diameter, 0.050 inch). Since the vein is always filled, blood frequently pours from the vessel the moment the needle point penetrates the wall. Unless the insertion is made rapidly the blood may obscure vision; therefore, it is desirable to insert the needle as rapidly as possible.

12. At this point, the major technical problems have been overcome. Once the artery needle is in place it should not produce any problems. The venous needle, on the other hand, has to be watched carefully until the vein becomes refilled. The venous wall has a tendency to collapse over the bevel of the needle and fluid will not flow out of the tubing. This can be prevented or corrected by gently changing the angle of the needle inside the vessel.

13. Perfusion of material can be accomplished in either of two ways:

A. By the use of a syringe attached to the arterial tubing. This is adequate if short experiments are carried out or small volumes perfused. The major difficulties with this method are the problems of maintaining a constant rate of flow and pressure and the fact that the temperature of the perfusing material in the syringe is influenced by room temperature.

B. Both of these problems can be overcome by using a constant circulation pump* (Fig. 1). With this method the intake

(arterial) end of the tubing is placed in a graduated cylinder kept immersed in the water bath. The perfusion fluid is pulled up into the tubing and forced through the pump in a pulsating fashion. By keeping the tubing between the pump and the animal under the surface of the water as much as possible the temperature of the perfusing fluid remains constant. As shown in Fig. 1, the tubing is held in place by means of small clay balls.

14. Collection of perfused solutions can be made in test tubes on a time basis (Fig. 1), or if recirculation is considered necessary the venous tubing may be placed in the cylinder. This results in constant circulation and recirculation of the perfusion solution.

15. The rate at which material flows through the placenta can be determined by counting drops and measuring the volume from the venous side. With practice it is possible to relate number of drops per unit time to volume. If the flow rate is too slow the speed of the pump can be increased; the converse is equally true. When the pump is first started the flow rate is sometimes fairly rapid. As soon as the perfused material is reasonably free of red cells the rate slows down to a fairly constant flow. Once the flow rate has become constant the whole procedure becomes semiautomatic and will generally continue successfully for the duration of the experiment.

Comment

The respiratory and nutritive elements of the placenta appear to be dependent on the maternal circulation. Therefore, it seemed unnecessary to oxygenate the perfusing material. This greatly simplifies the complexity of the apparatus described above. Although the present technique requires careful attention to detail, once it is mastered few major problems are encountered. It is important, however, to emphasize that not only are details significant but the sequence in which the apparatus is put together is equally important. The most satisfactory

*Peristaltic action pump made by American Instrument Co., Inc. Silver Spring, Maryland.

and effective procedure we have found is the one presented above. With this procedure more than 100 successive experiments have been successfully completed.

There are several major advantages of such a technique in studying placental physiology and biochemistry.

1. Fetal metabolism is eliminated. In studying the transport of rapidly metabolized materials, without this technique, one risks attributing the effects of fetal metabolism to placental function. We have encountered this problem in the study of estrogen transport.² Results could not be accurately interpreted until the present technique was used.

2. Serial samples may be taken from the fetal side of the placenta so that kinetics of transport from mother to fetus can be determined.

3. It is possible to introduce modifying influences, after a control period, and study their effects in the same animal. This we

have found to be of advantage in a study of carbohydrate transport.

4. A comparison can be made of the transport of materials from maternal to fetal circulation and equally well in the opposite direction.

Summary

A technique for the *in situ* study of placental transport in the pregnant guinea pig has been developed. The procedure involves removal of the fetus from the uterus into a saline-filled bath with the placenta remaining in its normal position. Perfusion solutions are circulated from the fetal side of the placenta through an umbilical artery and collected from the umbilical vein. Test substances are added to the perfusion solution or injected into the mother and collected from the fetal side of the placenta. Although the technique is relatively simple, many technical problems are involved. These have been discussed and their solutions described.

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Transfer of sodium and iodo-antipyrine across guinea pig placenta with an in situ perfusion technique

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THE rate of transfer of both radioactive sodium and antipyrine has been used as a measure of placental function in the human.^{1, 2} We have investigated some of the fundamentals involved in the transport of these substances with an in situ perfusion technique of guinea pig placenta.

Methods

The fetal side of the guinea pig placenta was perfused in situ as described in a previous paper.³ In the studies of transfer of I^{131} -labeled antipyrine (specific activity 0.1 mc. per milligram) 6 per cent dextran in saline was used as the perfusate and was circulated only once through the placenta. To investigate transfer from mother to fetus, the labeled antipyrine was injected into a

maternal jugular vein and the appearance of radioactivity in the "fetal circulation" was determined. In studies on transfer from fetus to mother, the antipyrine was added to the perfusing fluid and the loss in radioactivity during a single passage through the placenta was recorded. Radioactivity was determined in a well-type scintillation counter and reported in counts per minute (c.p.m.) above background per milliliter of perfusing fluid, or as total c.p.m. per unit time. The volume inflow and outflow of perfusing fluid was recorded in all studies.

In the experiments with Na^{22} only the transfer from fetus to mother was investigated. The approach was the same as described above except that in some studies guinea pig plasma was used as the perfusate. The specific activity of the sodium was 300 μ c per millimol.

Results

A total of 13 experiments were done on the transfer of antipyrine. The following are representative examples.

In Fig. 1 are presented the results of an experiment in which serial injections of labeled antipyrine were given intravenously to the mother. The concentration of radioactivity appearing in the perfusate demonstrates a recurrent pattern indicating no change in function in the transport of antipyrine for the duration of the experiment. The general shape of the curve is similar

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Presented in part in Survey of the Placenta and Fetal Membranes, Villee, C. A., editor, Conference held at Princeton, New Jersey, Nov. 9-11, 1958, by the Association for the Aid to Crippled Children.

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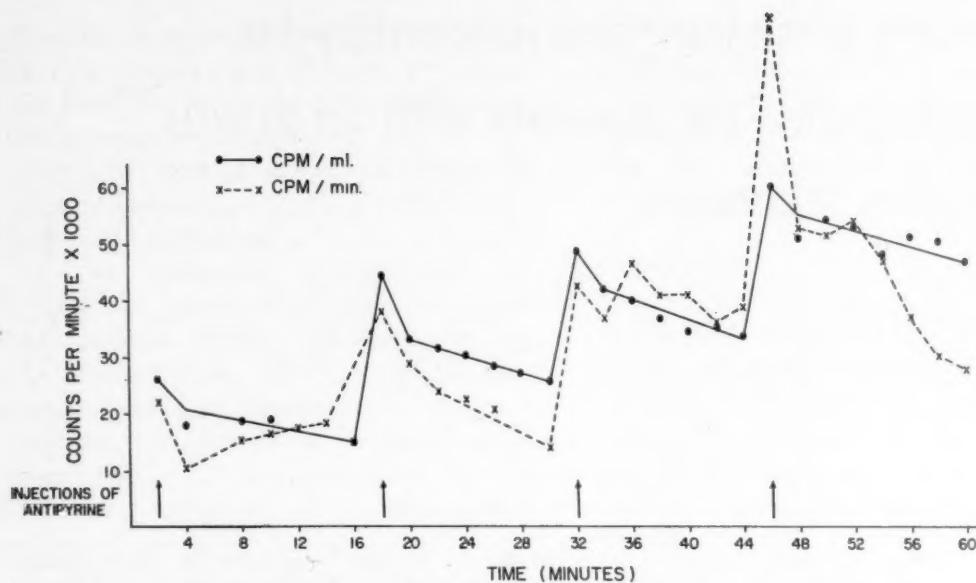


Fig. 1. Transfer of I^{131} antipyrine from mother to fetal side of the placenta. Serial injections of I^{131} antipyrine were made into the maternal jugular vein and the appearance of radioactivity in the perfusate of the fetal side of the placenta was measured as counts per minute per milliliter of perfusate and counts per minute per minute of perfusion.

to that following the intravenous injection of antipyrine for determination of total body water and is probably a reflection of the maternal levels of antipyrine. In contrast to the regular patterns for the concentration of radioactivity in the perfusate, the total amount of radioactivity transferred per minute is irregular and appears related to flow rate.

The dependence of total transfer on flow rate is better demonstrated in Fig. 2. This applies to transfer in both directions (the amount of iodo-antipyrine transferred per minute is in direct proportion to the flow rate). With the higher flow rates there was, moreover, a significant loss in volume of the perfusing fluid. Both methylene blue and a solution of albumin tagged with Evans blue (T-1824) were added to the perfusate and no external leaks could be detected. It is assumed that water was transferred through the placenta as a result of increased pressure coincidental with the increased flow rate. The total transfer of iodo-antipyrine was not influenced by the net flow of water except through the effect on outflow rate.

In a second series of experiments the

pressure in the perfusion circuit was raised by elevating the outflow catheter. The catheter was raised until the outflow rate was reduced to half although the inflow rate was maintained unchanged. This resulted in a considerable net flow of fluid from the fetal to the maternal circulation. The results (Fig. 3) are similar to those obtained with alterations in flow rate. Following a short period of readjustment, the concentration of I^{131} antipyrine returned to its former level. This was unaffected by the net flow of water. The total transfer of iodo-antipyrine paralleled the outflow rate.

The effect of flow rate on the transfer of sodium across the placenta from fetus to mother was investigated in 6 guinea pigs. In one experiment dextran was used as the perfusate. There was a progressive increase in permeability to sodium during the course of the experiment which obscured the effect of variations in flow rate. In 2 experiments there were technical problems in controlling flow rate. The results in these were similar but not as clear-cut as in the final 3 experiments which are presented in Table I. The milliequivalents of sodium transferred is

Table I. Effect of flow rate on the transfer of sodium across the placenta from the fetal side

	Flow rate		
	ml./minute	mEq./ml.	mEq./minute
I	2.1	0.0398	0.0820
	0.7	0.0665	0.0430
	1.7	0.0556	0.0916
II	0.3	0.0806	0.0242
	0.8	0.0403	0.0342
	0.45	0.0570	0.0256
III	1.0	0.0589	0.0600
	0.25	0.1082	0.0243
	1.4	0.0413	0.0578

calculated by multiplying the fall in radioactivity following the perfusion by the specific activity of the sodium (c.p.m. per mEq. Na). The slower the flow rate the more complete is the transfer (or exchange) per unit volume. However, the faster the flow rate, the larger the transfer (or exchange) per unit time.

In studies on the transfer of other materials in which dextran in saline was used as perfusate, sodium transfer was often extremely high and the values varied greatly from experiment to experiment. With 5 per cent human albumin in isotonic saline the results were more consistent but there was

often a progressive increase in permeability during the course of an experiment. In Table II are presented the results of an experiment with albumin in saline as the perfusate in which the transfer of sodium and D-xylose were measured. There is a progressive increase in the permeability of the placenta to both substances. This did not occur when guinea pig plasma was used as the perfusate. In the reported experiments on flow rate (Table I), guinea pig plasma was the perfusate.

Comment

Iodo-antipyrine moves extremely rapidly through membranes despite its relatively large molecular weight apparently because of its lipid solubility.⁴ The results of our experiments with iodo-antipyrine are typical of a rapidly equilibrating substance. Transfer per unit volume is unaffected by flow rate, pressure changes, and direction of net water flow, indicating that the antipyrine has reached equilibrium concentration. Thus, the total amount of iodo-antipyrine transferred across the placenta per unit time becomes a direct measure of flow rate, at least within the limits used in these experiments.

In the experiment presented in Fig. 2 on

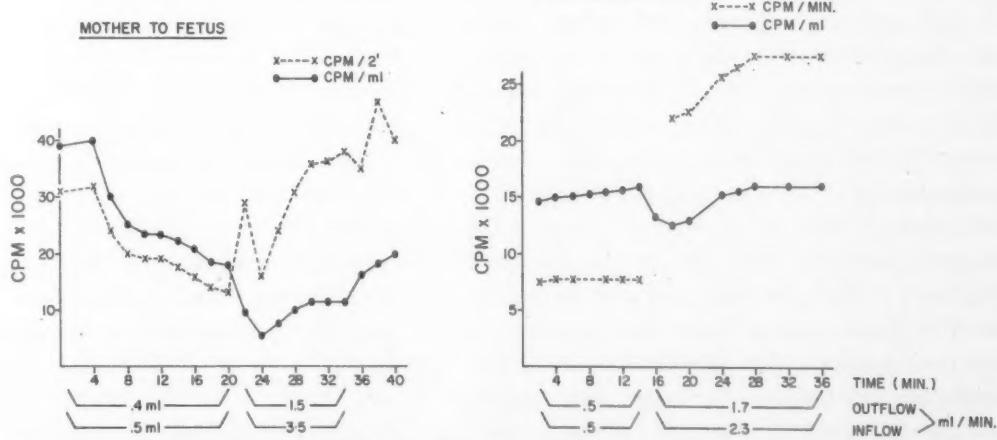


Fig. 2. The effect of flow rate on the placental transfer of I^{131} antipyrine. Transfer per milliliter perfusate is unaffected; transfer per unit time varies directly with flow rate.

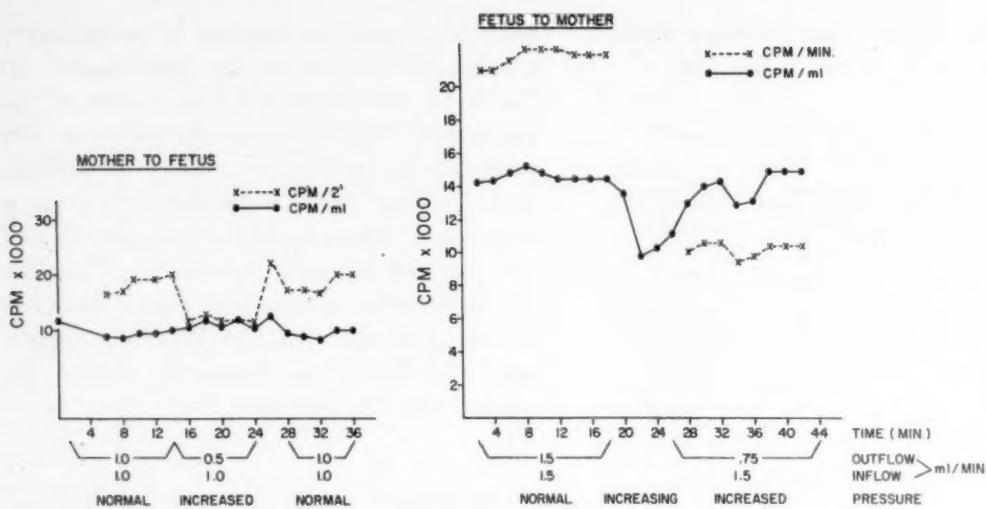


Fig. 3. The effect of pressure changes on the transfer of I^{131} antipyrine. The transfer per milliliter perfusate is unaffected; transfer per unit time drops with an increase in pressure, reflecting the fall in outflow rate.

the transfer of iodo-antipyrine from fetus to mother, the level of radioactivity in the perfusate before perfusion was 18,000 c.p.m. per milliliter. After a single cycle through the placenta the radioactivity fell to 3,000 c.p.m. per milliliter indicating that 15,000 c.p.m. per milliliter had been transferred across the placenta. This remained unchanged, excluding a short period of adjustment, even when the flow rate was increased three- to fourfold. Using a phraseology common among physiologists, the proportion of iodo-antipyrine extracted from each milliliter of perfusate, the extraction ratio, was constant despite changes in flow rate. The most likely explanation for this constancy is that all of the iodo-antipyrine presented to the placental membrane was transferred across, and this occurred at both flow rates. The iodo-antipyrine left in the perfusate following perfusion (3,000 c.p.m. per milliliter) could be accounted for if 16 per cent of the fetal perfusate passed through vascular shunts or arteriovenous anastomoses and, therefore, was not available for "extraction" into the maternal circulation. A similar observation relative to oxygen transfer across sheep placenta has been made by Dawes,⁵ and anatomical studies of human placenta have

suggested the presence of vascular shunts.⁶

Although the extraction ratio for iodo-antipyrine was constant in each experiment, it varied from a low of 50 per cent to a high of 85 per cent in different experiments. It is not clear what caused this variability but some possibilities can be suggested. A certain amount of physiological variation may be expected and this may have been exaggerated by differences in the stage of gestation since this was not accurately controlled. The extensive manipulation involved in the technique may contribute artefacts. An artefact intrinsic in the technique is that only one umbilical artery is cannulated. Despite this, if dye is added to the perfusate, the entire placenta becomes colored, indicating anastomotic connections between both halves of the placenta. Anatomical variations in these anastomoses could easily influence the amount of perfusate presented to the placental membrane for extraction.

Sodium equilibrates across the placenta more slowly. With slower flow rates, more time is permitted for equilibration and therefore more sodium is transferred per unit volume. At the higher flow rates although less sodium is transferred per unit volume, more is transferred per unit time. This is the result of the more steeply main-

tained gradient throughout the period allowed for transfer. Thus, the amount of sodium transferred is affected by flow rate but sodium is not as sensitive an indicator of flow rate as antipyrine.

Although the relatively slow equilibration of sodium limits its use as a measure of flow rate, it is a better measure of the condition of the placental membrane. This is suggested by other observations made in the course of these experiments. Dextran in saline was used as the perfusing medium in the initial experiments with Na^{22} because of its easy availability. It quickly became evident that the results were erratic and at times sodium transfer was excessively rapid. With 5 per cent human albumin in saline, the results were somewhat more consistent but it was common to find an increasing permeability to sodium during the experiment. This was also true with carbohydrate (Table II). For this reason, guinea pig plasma was used as the perfusing medium in subsequent sodium experiments with more constant and easily interpretable results. This type of experience has been had by others using the perfusion technique and appears to result from the removal of a protective protein lining of the membrane which is ordinarily maintained by plasma globulins. Chambers and Zweifach⁷ found the relative protective efficiency of various colloids to be blood serum > bovine albumin > gelatin > acacia.

Flexner and his associates⁸ have studied the transfer of sodium across the placenta

from mother to fetus in the intact guinea pig and found that near term it was 6.1 mg. per gram of placenta per hour. Since this transfer rate far exceeds the net transfer of sodium to the fetus, it must be assumed that sodium is being transferred in the reverse direction at almost the same rate. The transfer rates of the perfused placenta in the present study approximate Flexner's figure only at flow rates of less than 1 ml. per minute. This is considerably less than the estimated flow rate of guinea pig placenta of 2.5 ml. per minute.⁹ One possible explanation of this difference is that the release of intrauterine pressure involved in exposing the placenta for the perfusion technique results in dilatation of the placental vessels and an increased permeability.

It has been assumed in the experiments on transfer from fetus to mother that disappearance of radioactivity from the perfusate is equivalent to transfer across the placenta. The only alternative would be retention in the placenta. In 3 experiments with radioactive sodium, the amount of radioactivity remaining in the placenta and in the perfusate trapped in the placenta was determined at the end of the experiment. It amounted to 10 to 15 per cent of the radioactivity that had disappeared from the perfusate in the course of the experiment, a figure that would not significantly alter the results or the conclusions.

Bauman and his co-workers¹⁰ have studied the rate of disappearance of Na^{24} on passage through the pulmonary circulation and found that 10 to 20 per cent of the radioactivity disappears in one cycle. This is much slower than occurs in muscle. It is suggested that this slow rate of exchange of electrolytes across the pulmonary capillaries may be related in some fashion to the primary function of the lung, the exchange of gases. It is interesting that in the placenta, where gaseous exchange is also a primary function, there is also a relatively slow exchange of sodium. In experiments in which we have maintained a flow rate approximating the estimated normal of 2.5 ml. per minute, the rate of sodium ex-

Table II. Perfusion of guinea pig placenta with 5 per cent albumin in saline

Time (minutes)	ΔNa^{22} (c.p.m./ml.)*	$\Delta\text{D-xylose}$ (mg./ml.)*
4	780	0.24
12	1205	0.34
24	1036	0.37
36	2084	0.71
48	3068	0.94
60	2970	1.04

*The fall in concentration of Na^{22} and D-xylose in the perfusate following one cycle through the placenta. There is a progressive increase in permeability of the placenta during the experiment.

change has commonly been 20 to 30 per cent. As noted above, this figure is probably higher than that found under normal intrauterine conditions. Similarities in the pharmacological reactions of the pulmonary and placental circulations have also been commented upon.¹¹

Summary

The transfer of I¹³¹ antipyrine across the guinea pig placenta was measured with the technique of *in situ* perfusion. The amount transferred per unit volume of perfusate was not affected by alterations in flow rate or intravascular pressure. The amount of

radioactivity transferred per unit time was therefore proportional to the flow rate and served as an accurate index of blood flow. The amount of sodium transferred across the placenta from fetus to mother was measured with Na²² as tracer. The transfer per unit volume varied inversely with the flow rate while transfer per unit time varied directly with flow rate. Radioactive sodium provides a less accurate measure of flow rate than antipyrine, but is a better indicator of the permeability of the placental membrane.

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Transfer of carbohydrates across guinea pig placenta

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THE development of a technique for in situ perfusion of guinea pig placenta has made it possible to study the transfer of materials from fetus to mother under relatively well-controlled conditions.¹ In this paper will be presented the results of application of this technique to the problem of carbohydrate transport.

Methods

The technique of placental perfusion is described in detail in a previous paper.¹ In brief, an umbilical artery and the vein are cannulated at hysterotomy and an artificial circulation established with the aid of a pump and a reservoir of plasma diluted with equal parts of saline. In the experiments to be described, an "open circuit" was used; the plasma passed through the placenta only

once and was not recirculated. Flow rate was maintained at about 1 ml. per minute. The inflow plasma contained the carbohydrate under examination in a concentration, as a rule, of 2 mg. per milliliter. In the experiments with glucose, higher concentrations were used to be certain that a fetal-maternal gradient was established. The difference between inflow and outflow plasma of the concentration of carbohydrate was taken as a measure of placental transfer into the maternal circulation. This was a reasonable inference since analysis of the placenta failed to reveal any significant accumulation of the carbohydrate in the placenta, and the amounts involved were far too great for placental metabolism to contribute significantly.

Relative rates of transfer were established by investigating more than one carbohydrate in each experiment. At the beginning of the experiment, a period of equilibration of 5 to 10 minutes was permitted to elapse before perfusing with test materials. The test solution was perfused through the placenta for 4 minutes before the beginning of collections of outflow plasma in order to clear the channels of the previous test solution.

Solutions of alpha and beta glucose were prepared immediately before perfusion to avoid the effects of spontaneous mutarotation. The alpha-beta glucose solution was prepared from alpha glucose an hour before the experiment to permit time for mutarotation to reach equilibrium prior to perfusion.

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**John and Mary Markle Scholar in Medical Science.*

Analytical methods

Glucose was determined by the method of Nelson² and Somogyi.³ To determine galactose and the pentoses, we first removed the glucose by fermentation with yeast. This was done by adding a 1:10 suspension of baker's yeast to 5 ml. of the protein-free filtrate and incubating at 30° C. for one hour or at room temperature for 4 hours. Standards were run concurrently to correct for minor losses that took place with some of the pentoses during protein precipitation. Fructose was determined by the resorcinol method.⁴ Glucuronic acid was determined by the method of Dische.⁵

Results

In Table I are presented the relative transfer rates of 5 pentoses. The transfer rate of D-xylose is consistently higher than that of L-xylose, while those of the other 3 pentoses tend to fall between these extremes. In general the transfer rates are D-xylose >D-lyxose >L-arabinose >D-ribose >L-xylose.

The transfer rates of the hexoses are presented in Tables II and III. These are calculated as net transfer rates as suggested by Karvonen and Räihä.⁷ This was done in an attempt to correct for variations in the fetus-to-mother gradient for glucose introduced by variations in maternal blood sugar in the different experiments. To obtain the net transfer rate, the fall in concentration of the carbohydrate in the perfusate is multiplied by the reciprocal of the gradient between the fetal and maternal concentrations.

Table I. Transfer of pentoses from fetus to mother*

Experiment	D-xylose	L-xylose	D-lyxose	D-ribose	L-arabinose
1	0.59	0.29	0.27	0.05	
2	0.45	0.18	0.58	0.27	0.29
3	0.95	0.21	0.48	0.30	0.43
4	1.21	0.48			0.77
5	0.47	0.16			0.61
6	0.92	0.34	0.57	0.39	0.35

*The fall in concentration (milligrams per milliliter) of each carbohydrate in the perfusate during a single passage through the placenta.

Table II. Transfer of hexoses from fetus to mother

Experiment	α glucose	β glucose	$\alpha\beta$ glucose	Fructose
1	0.64	0.69	0.57	0.02
2	0.27	0.29	0.26	0.07
			0.37	0.13
			0.17	0.04

Table III. Transfer of hexoses from fetus to mother*

Experiment	Glucose	Galactose	Glucuronic acid
1	0.34		0
2		0.23	0
3	0.11	0.11	0

*Transfer rate = $\frac{\text{fall in perfusate concentration}}{\text{fetal concentration - maternal concentration}}$ \times

The transfer rate of fructose is extremely low and no transfer of glucuronic acid was detectable. There was no evident difference in transfer rates among alpha and beta glucose and the equilibrium mixture of alpha-beta glucose.

Comment

There is already considerable evidence that the transfer of carbohydrates across the placenta involves a transport mechanism and cannot be explained entirely by simple diffusion. Widdas reached this conclusion after an analysis of the kinetics in transfer across sheep placenta.⁶ Karvonen and his co-workers demonstrated a significant difference in transfer rates of glucose and fructose across the placenta in the guinea pig⁷ and in the human.⁸ Colbert and co-workers⁹ found that the infusion of glucose into the pregnant rabbit reduced the rate of transfer of sorbose, suggesting competition for a carrier system.

The present study discloses a significant difference in transfer rates between the stereo-isomers D-xylose and L-xylose. Such stereo-specificity is commonly involved in enzymic reactions and in specific transport mechanisms. The very slow transfer rate of the keto-hexose, fructose, is also confirmed.

The variability in rates of transfer from experiment to experiment has been previously noted and discussed relative to sodium and iodo-antipyrine.¹⁰ This limits comparison between experiments. However, the relative rates within each experiment are reasonably reproducible.

The nature of the carrier system for carbohydrates that exists at membranes has not been identified despite considerable investigation. It is not unlikely that there is a basic similarity in the transport process for carbohydrates at membranes; however, differences in the relative rates of transfer of carbohydrates at various membranes suggest individual differences. Many attempts have been made to relate the variations in rates of transfer to the configuration of the carbohydrate without consistent results. The most recent of these¹¹ suggests that the three-dimensional configuration, C₁, is a primary requisite for enzymic and transport mechanism, and has presented evidence that this is true for the red blood cell. This concept has not yet been widely applied but appears in general to fit our data.

Keston¹² has attempted to relate the transport mechanism to the activity of mutarotase. This enzyme is capable of interconverting alpha and beta glucose. For this reason the transfer rates of alpha and beta glucose were investigated. No difference was found, offering no support for the theory, but, on the other hand, not excluding it.

A minor point of interest was noted in the previous paper¹⁰ (Table II). When albumin in saline was used as perfusate, a progres-

sive increase in the transfer of sodium occurred during the course of the experiment, paralleled by a similar increase in the transfer of D-xylose. This suggests a common step in the transport of both substances.

The transfer of glucuronic acid was investigated because of a recent study from this laboratory demonstrating a relative impermeability of the placenta to the glucuronide conjugates of estrogens.¹³ There was no detectable transfer during the course of the experiment. It was not a surprising finding because highly charged anions are known to penetrate membranes slowly.¹⁴ This may contribute to the impermeability of estrogen glucuronides.

Summary

1. The transfer of carbohydrates across guinea pig placenta from fetus to mother has been investigated with use of an *in situ* perfusion technique.
2. The transfer rates of pentoses appear to be controlled by a stereo-specific mechanism. Thus, D-xylose was consistently transferred at a much faster rate than L-xylose.
3. Among the hexoses, fructose was transferred slowly, and glucuronic acid not at all. The latter may contribute to the relative impermeability to glucuronide conjugates.
4. No difference was demonstrable in the transfer rates of alpha and beta glucose.

The carbohydrates were obtained from Mann Laboratories, New York City. A sample of beta glucose was donated by Dr. A. S. Keston.

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Effects of anoxia on the metabolism of the human placenta in vitro

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THE ability to survive prolonged deprivation of oxygen, characteristic of fetal tissues, decreases rapidly after birth. The experiments of Himwich, Bernstein, Herrlich, Chesler, and Fazekas¹ suggested that survival of the newborn rat in anoxia is dependent upon the energy derived from glycolysis.

Placenta and fetal tissues are related in many ways and it was of interest to investigate the behavior of term placenta in anoxia.

Methods

Samples of human term placenta were obtained within 15 minutes after delivery and placed in ice-cold 0.9 per cent sodium chloride. Aliquots were taken for analysis of glycogen content. Slices of tissue were quickly weighed on a torsion balance and placed in Warburg vessels in 3.0 ml. of a medium containing, per milliliter, 40 micromoles K⁺, 80 micromoles Na⁺, 10 micromoles Mg⁺⁺, 100 micromoles Cl⁻, and 40 micromoles of phosphate, with an initial pH of 7.1.

The appropriate C¹⁴-labeled substrate (uniformly labeled glucose or fructose or potassium pyruvate-2-C¹⁴) was placed in the sidearm of the Warburg vessel and tipped into the main reaction chamber after the

flasks had been flushed with nitrogen or oxygen for 7 minutes.

The initial concentration of the C¹⁴-labeled substrate in the incubation medium was 10 micromoles per milliliter. The slices were incubated with shaking for two hours at 37° C.

After the incubation, the slices of tissue were blotted gently on filter paper, weighed, and extracted for the measurement of total lipids according to the method of Folch, Lees, and Sloane-Stanley.² An aliquot of the tissue slice after incubation was analyzed for glycogen as described by Walaas and Walaas.³ Aliquots of the incubation medium were analyzed for glucose,⁴ fructose,⁵ pyruvate,⁶ and lactate.⁷ Other aliquots of incubation medium were used for C¹⁴ analyses.¹⁴

The respiratory carbon dioxide from the alkali present in the center well of the Warburg flask was precipitated as barium carbonate, which was then washed and transferred to stainless steel planchets for C¹⁴ analyses.

Radioactivity was measured in a windowless proportional flow counter and corrected for self-absorption. Each sample was counted long enough to reduce the probable error of counting to less than 7 per cent with pyruvate as substrate and 3 per cent with glucose or fructose as substrate.

Results

A. Pyruvate-2-C¹⁴ metabolism by human term placenta. The results listed in Table I show that the utilization and the produc-

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tion of pyruvate and lactate by human term placenta is greater in nitrogen than in oxygen ($P < 0.01$). The incorporation of pyruvate into glycogen is small, but is greater in oxygen than in nitrogen ($P < 0.01$). The utilization of pyruvate and its conversion to CO_2 were less in anoxia.

Lipid synthesis from pyruvate proceeds at the same low rate in nitrogen and in oxygen. A single measurement by the indirect method⁸ gave 1.5 as respiratory quotient; this agrees with the respiratory quotient of 1.5 calculated from the weight of the carbonate recovered from the center wall of the Warburg vessel. Tissue slices incubated in an oxygen atmosphere produce less pyruvate than lactate, which suggests a rapid utilization and conversion of pyruvate to other metabolites. In nitrogen, pyruvate production is greater and pyruvate utilization is less. No glucose is produced by the placenta slice in either oxygen or nitrogen. This confirms earlier observations from this laboratory.⁹

B. Metabolism of uniformly labeled glucose or fructose by human term placenta. Further evidence of increased glycolysis by the tissue slice in an atmosphere of nitrogen appears in Table II. The accumulation of lactate is greater with glucose as substrate than with fructose as substrate in both oxygen and nitrogen. Fructose is produced under aerobic condition. This confirms previous findings.¹⁰ In anoxia, there is a net utilization of fructose. Lipogenesis from fructose is the same in oxygen or nitrogen

(0.07 micromoles per gram, wet tissue per 2 hours).

C. Metabolism of developing liver and placenta adjusted to content of ribonucleic acid. Because the water and connective tissue content varies not only among different organs but also in the same organ at different stages of development, metabolic comparisons on a basis of wet or dry weight may be misleading. The total amount of ribonucleic acid is an indirect estimate of the active cytoplasm of the placenta as the RNA is localized mostly in the placental cytotrophoblast.¹¹ Olmsted¹² has given the following values which, when converted to dry tissue weight, are: fetal liver 13-20 weeks, 26.2 mg. of RNA per gram of dry tissue weight; fetal liver 38 weeks, 27.6 mg.; adult liver, 19.9 mg.; term placenta, 10.4 mg.; young placenta, 13.7 mg.

There are no striking differences between the metabolic activities of liver and placenta with the three substrates (Tables III and IV). The quantity of metabolites produced is roughly equivalent in the two organs. The content of glycogen in the placenta is low.

Fructose, as measured chemically, is produced by the term placenta incubated in oxygen. Nevertheless, the production of labeled lipids and CO_2 indicates some utilization of fructose. The chemical method, of course, measures only the net utilization or production of fructose.

The rate of conversion of the three substrates to CO_2 is less in both young and term

Table I. Metabolism of pyruvate by slices of human term placenta (substrate: potassium pyruvate-2-C¹⁴)

	<i>Incubation in oxygen</i>	<i>Incubation in nitrogen</i>	<i>P</i>
Oxygen consumption	15.5 ± 0.4 (59)*	-	
Respiratory quotient	1.5 ± 0.1 (17)	-	
Glycogen utilization	2.8 ± 0.1 (39)	0.7 ± 0.2 (39)	< 0.01
Pyruvate utilization	21.7 ± 1.0 (57)	11.5 ± 0.9 (50)	< 0.01
Pyruvate production	4.8 ± 2.1 (23)	21.0 ± 3.2 (17)	< 0.01
Lactate production	17.4 ± 0.6 (47)	22.0 ± 0.8 (44)	< 0.01
Glucose production	0	0	
Conversion of labeled carbon to CO_2	1.0 ± 0.1 (30)	0.29 ± 0.05 (25)	< 0.01
Conversion of labeled pyruvate to lipids	0.03 ± 0.01 (6)	0.03 ± 0.01 (6)	--

*The numbers are the mean ± the standard error of the mean. The numbers in parentheses represent the number of determinations. All values except the respiratory quotient are expressed as micromoles per gram of wet weight per 2 hours of incubation at 37° C. The Student "t" test was utilized to compare averages.

placenta than it is in fetal and adult liver.

Lipid synthesis from pyruvate or fructose is the same in oxygen and in nitrogen in young and term placenta, respectively. Fetal lipogenesis is decreased fifteenfold in nitrogen. Adult liver lipogenesis is decreased 0.7 times by anoxia (Tables III and IV).

The ratio of the amount of lactate produced to pyruvate produced is an indirect measurement of the DPNH available for the transformation of pyruvate to lactate, catalyzed by lactic dehydrogenase (Table V).

Comment

Villee⁶ provided evidence during in vitro incubation that young and term placenta slices utilize glucose or pyruvate and produce lactate.

The present experiments confirm these findings and show that fructose is metabolized in the cell as estimated by the production of lactate and conversion of labeled fructose to CO₂ and lipids. Fructose utilization is much greater in nitrogen than in oxygen. It could be that in nitrogen, the permeability of cell membranes being increased, more fructose is able to enter the cell.

Previous studies of the mechanism of fructose production by human placenta¹³ showed that whole homogenates of placental tissue produced fructose. Fructose-6-phosphate is cleaved by the action of a nonspecific phos-

phatase at pH 9 to fructose and glucose. These observations can be correlated with our present findings in placental slices. Fructose is converted to fructose-6-phosphate by hexokinase activity and, then, within the cell is metabolized to lactate or CO₂, or is incorporated to lipids. It may be split to fructose and inorganic phosphate by the action of the nonspecific phosphatase.

Lactate production is much greater in oxygen or nitrogen when glucose is used as substrate instead of fructose. Hexokinase activity is greater with glucose than with fructose and more glucose-6-phosphate is formed than fructose-6-phosphate during the process of phosphorylation. In support of this assumption glucose utilization is 22.0 micromoles, whereas fructose utilization is 7.7 micromoles in nitrogen.

Glycolysis, as measured by lactate production, glycogen utilization, or pyruvate production or with any of the three substrates was twice as rapid in nitrogen as in oxygen. Villee and associates,¹⁴ studying the metabolism of fetal tissues from both rats and humans, demonstrated a fourfold increase in glycolysis during anoxia as estimated by lactate and pyruvate production. Fetal tissues increase their rate of glycolysis in nitrogen atmosphere more easily than does term placenta.

In oxygen, pyruvate is transformed to

Table II. Metabolism of uniformly labeled fructose or glucose by slices of human term placenta

	<i>Uniformly labeled fructose</i>		<i>Uniformly labeled glucose</i>	
	<i>Incubation in oxygen</i>	<i>Incubation in nitrogen</i>	<i>Incubation in oxygen</i>	<i>Incubation in nitrogen</i>
Oxygen consumption	18.0 ± 0.8 (8)*	—	18.6 ± 0.5 (4)	—
Glycogen utilization	1.4 ± 0.5 (4)	2.0 ± 0.4 (4)	1.1 ± 0.2 (2)	1.6 ± 0.07 (2)
Conversion of labeled fructose to glycogen	0.4 ± 0 (2)	0	—	—
Fructose utilization	3.7† ± 0.4 (8)	7.7 ± 1.9 (8)	—	—
Glucose utilization	—	—	22.1 ± 2.4 (4)	27.0 ± 1.4 (4)
Lactate production	15.5 ± 1.1 (6)	29.0 ± 1.3 (6)	26.6 ± 1.0 (4)	49 ± 1.0 (4)
Conversion of labeled fructose or glucose to CO ₂	0.17 ± 0.1 (8)	0.03 ± 0.06 (8)	0.14 ± 0 (4)	0.03 ± 0 (4)

*The numbers are the mean ± the standard error of the mean. The numbers in parentheses are the numbers of determinations. All values are expressed as micromoles per gram of tissue wet per 2 hours of incubation at 37° C. Student "t" tests were utilized to compare averages and all nitrogen values are different from oxygen values: P < 0.01.

†Net production of fructose.

Table III. Metabolism of developing organs adjusted to ribonucleic acid content for each tissue (substrate: potassium pyruvate-2-C¹⁴)*

	13-20 weeks, fetal liver		38 weeks, fetal liver		20 weeks, placenta		40 weeks, placenta	
	Oxygen	Nitrogen	Oxygen	Nitrogen	Oxygen	Nitrogen	Oxygen	Nitrogen
Oxygen consumption	6.6	--	6.0	--	8.5	--	6.0	
Glycogen utilization	8.7	15.5	28.7	37.2	--	--	1.0	1.4
Pyruvate production	4.5	7.9	1.0	1.7	11.3	16.1	1.8	8.0
Pyruvate utilization	6.4	4.8	6.5	6.1	5.0	9.0	8.3	4.3
Lactate production	5.4	12.6	4.8	9.1	6.4	10.5	6.6	8.4
Conversion of labeled carbon of pyruvate to CO ₂	4.3	0.9	0.2	0.002	1.1	0.09	0.38	0.11
Conversion of labeled carbon of pyruvate to lipids	0.23	0.013	0.028	0.002	0.11	0.08	0.011	0.011
Ribonucleic acid (milligrams per gram dry weight tissue†)	26.2		27.6		13.7		10.4	

*The values for fetal liver and young placenta are borrowed from Villee, Hagerman, Holmberg, Lind, and Villee²⁴ and expressed in micromoles per milligram of ribonucleic acid per hour of incubation at 37° C.

†Olmsted.

Table IV. Metabolism of developing organs adjusted to the content of ribonucleic acid in each organ*

	Uniformly labeled fructose				Uniformly labeled glucose					
	Fetal liver		Term placenta		Fetal liver		Term placenta		Adult liver	
	Oxygen	Nitrogen	Oxygen	Nitrogen	Oxygen	Nitrogen	Oxygen	Nitrogen	Oxygen	
Oxygen consumption	5.9		6.9	--	1.0	--	0.8	--	1.4	--
Glycogen utilization	7.6	10.6	0.55	0.80	2.0	2.5	0.06	0.08	5.7	7.7
Hexose production	3.6	3.5	18	18.4	0.49	0.53	1.13	0.65	2.5	3.6
Hexose utilization	--	--	--	--	0	0.45	1.1	1.3	0.75	0.85
Fructose utilization	4.1	3.1	1.5†	3.2	--	--	--	--	--	--
Lactate production	2.8	8.8	6.5	12.1	0.64	1.9	1.3	2.5	1.0	1.9
Conversion of carbon of labeled hexose to CO ₂	0.07	0.003	0.06	0.008	0.0015	0.0003	0.007	0.001	0.01	0.005
Conversion of carbon of labeled hexose to lipid	0.034	0.006	0.024	0.021	0.08	0.001	--	--	0.007	0.005

*The values for fetal and adult liver are borrowed from Villee, Hagerman, Holmberg, Lind, and Villee.²⁴ All values are expressed in micromoles per milligram of ribonucleic acid per hour of incubation at 37° C.

†Fructose production.

acetyl coenzyme A and, by condensation with oxaloacetic acid, enters the Krebs cycle. In nitrogen, pyruvate utilization decreases because oxydative enzymes (cytochromes and cofactors as TPN and DPN) are reduced. In this condition the tissue will metabolize pyruvate to lactic acid. During the process some DPNH is oxydized and the reaction ends when equilibrium between lactate and pyruvate is attained as in our experiments.

The observations reported here and by others indicate that both liver and placenta

have their own biochemical patterns. Under anaerobic conditions, term placenta is in general similar to adult liver in its rate of glycolysis and lipid synthesis. In terms of the amount of metabolites produced per unit of RNA, a rough estimate of the amount of the cytoplasm in the placenta, term placenta is as active aerobically as fetal liver or young placenta.

Both fetus and placenta are derived from one fertilized egg with the same genetic potential. Nevertheless, during the development, each organ seems to evolve its own

Table V

<i>Ratio</i>	<i>In oxygen</i>	<i>In nitrogen</i>
13 weeks fetal liver	0.8	2.6
38 weeks fetal liver	0.7	1.5
40 weeks placenta	0.8	1.9

metabolic pattern, depending in part on its environment and period of development.

Since term placenta is as active metabolically as the young or adult liver or young placenta, this weakens on a cellular level the old concept of placental senescence. The onset of labor cannot be based on a decrease of placental activity at term.

Summary

Term placental slices metabolize pyruvate, glucose, and fructose to lactate, lipids, and CO_2 like other human tissues. The utilization

of glucose or fructose by the placental slices indicates the presence of active hexokinases; only a minute amount of glucose is produced by the term placenta. Term placenta has rates of lipogenesis and glycolysis in nitrogen similar to adult liver.

The amount of metabolites produced by fetal and adult liver are about equal to those produced by term placenta in oxygen and nitrogen, when measured per unit of ribonucleic acid to adjust for the variations in the water content. On the basis of these results, biochemical placental senescence and onset of labor are discussed.

In contrast to the similarities summarized above, term placenta has its own patterns in some other aspects, namely, fructose production, low glycogen content, and glucose production. It is still fairly active at term.

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Effect of the placenta on the electrical activity of the cat uterus in vivo and in vitro

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THE placenta takes over in late pregnancy the function of the corpus luteum in maintenance of pregnancy, presumably by secreting progesterone.¹⁻³ The mechanism whereby progesterone acts to maintain pregnancy and prevent abortion has not been fully elaborated. Recently, it has been postulated that placental progesterone does not act only by the release of this hormone into the blood stream, but also acts locally to inhibit the overlying myometrium.^{2, 3} It has been proposed that this action is in part a result of alterations in muscle cell membrane properties leading to a decrease in intracellular potassium and an increase in intracellular sodium.^{2, 3}

If placental progesterone acts locally on the overlying myometrium to inhibit activation of these muscles by the stretch imposed by fetal growth, removal or decrease of the effect of placental progesterone could result in the onset of labor. The recent demonstration of remarkable alterations in myometrial sensitivity to Pitocin at term^{4, 5} would be explicable in terms of the previous evidence that progesterone treatment diminishes sensitivity to Pitocin⁶ and would suggest that progesterone-controlled alterations in the sensitivity of the responding uterus play a role in the onset of labor.

This possibility has been tested by recording the electrical activity of the uterus of the

cat in vitro and in vivo at various times during pregnancy. The spontaneous and Pitocin-induced electrical activity of the uterus has been studied at various recording sites in the uterus; over the placenta, over the fetus but not over the placenta, and over a nonfetal area. In addition, the possible chemical basis for differences in electrical activity was investigated by means of a study of uterine electrolytes from various areas of the uterus at various stages of pregnancy.

Methods

Electrodes. Previous experience in recording the electrical activity of the pregnant cat uterus in vitro with small pore electrodes⁷⁻⁹ suggested the importance of the use of a small pickup electrode. It was also essential to have an electrode which could be kept in place for several weeks and during labor. The solution eventually adopted was the use of sterling silver wires (0.016 inch in diameter) which were worked into disks 1 mm. in diameter and perpendicular to the wire at the tip. These wires were insulated with polyethylene except for this disk electrode. These disks were implanted into the uterus at various sites by carefully slitting open the serosa and working the disk into the slit. The slit was closed with a very fine thread. Six or 7 electrodes were labeled and implanted in each animal. The insulated silver wire leads were bent so as to minimize the tension exerted on the electrode and

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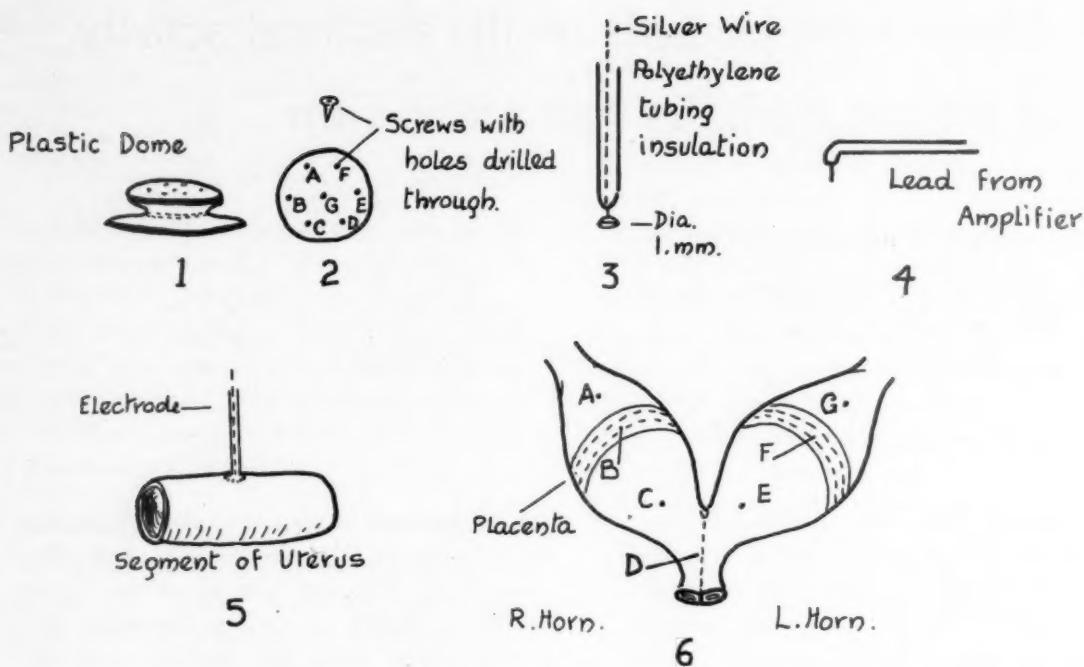


Fig. 1. Technique for recording of electrical activity of the cat uterus *in vivo*. 1, The plastic dome which was sewn between the shoulder blades. 2, Top view of plastic dome showing the screws to which the leads from the uterus were attached. Each screw had a hole drilled in it to permit insertion of the shielded leads from the amplifier. 3, The electrode and a short length of the insulated lead. The electrode was inserted through a slit under the uterine serosa and sewn into place by closing this slit around the electrode. The electrode in place is illustrated in 5. 4, A lead from the amplifier which fitted into the screw hole in the plastic dome. 5, Segment of uterus with the electrode in place. 6, The positions of the electrodes in the experiment from which the records in Figs. 5, 6, 7, and 8 were obtained. B and F electrodes were over the placenta. A, C, G, and E electrodes were as indicated except that G was actually in the same relative position depicted but on the next more proximal fetus. D electrode was on the cervix.

the wires were anchored by tying each of them separately in place as they emerged from the abdominal wall and by working them up through the subcutaneous tissues to a point between the shoulder blades. A plastic (Lucite) dome was sewn in place between the shoulder blades. The wire leads were then attached to labeled metal screws inserted in this disk. The leads from the amplifier were inserted into holes bored in these screws. When records were to be taken a ground electrode was inserted into the abdominal wall at a site chosen to minimize pickup of the maternal ECG. This procedure is diagrammed in Fig. 1.

Maintenance of animals and birth of young. The cats were unable to scratch or bite out the Lucite dome but showed no discomfort or irritation at its presence. Infec-

tions were prevented by the repetitive administration of antibiotics. All the 7 animals studied by this procedure carried their kittens to term except 2 which received large doses of Pitocin (> 1 unit) and which were subsequently found to have reabsorbed their young. Three of these animals delivered all their young alive without difficulty and were discovered only after delivery was completed.

Experimental procedure.

In vivo studies. A record was taken from each electrode immediately after completion of the initial operation to establish that electrical continuity existed. At this time action potentials were sometimes recorded at all electrodes. This activity presumably arose as a result of stimulation from the operative procedures. Electrical activity was rarely present in records taken about one week sub-

sequent to the operation. At this stage of the experiment the animals were usually one half to two thirds of the way through the gestation period. After the above control records were taken, Pitocin was injected in a dose of 0.025 to 0.25 unit intramuscularly and the effect of this on the occurrence of

action potentials at the various electrodes was noted. Similar experiments were run at about weekly intervals until parturition took place or until action potentials were induced by Pitocin at all electrodes, including those placed over placentas. At this point the animals were always at term and delivery oc-

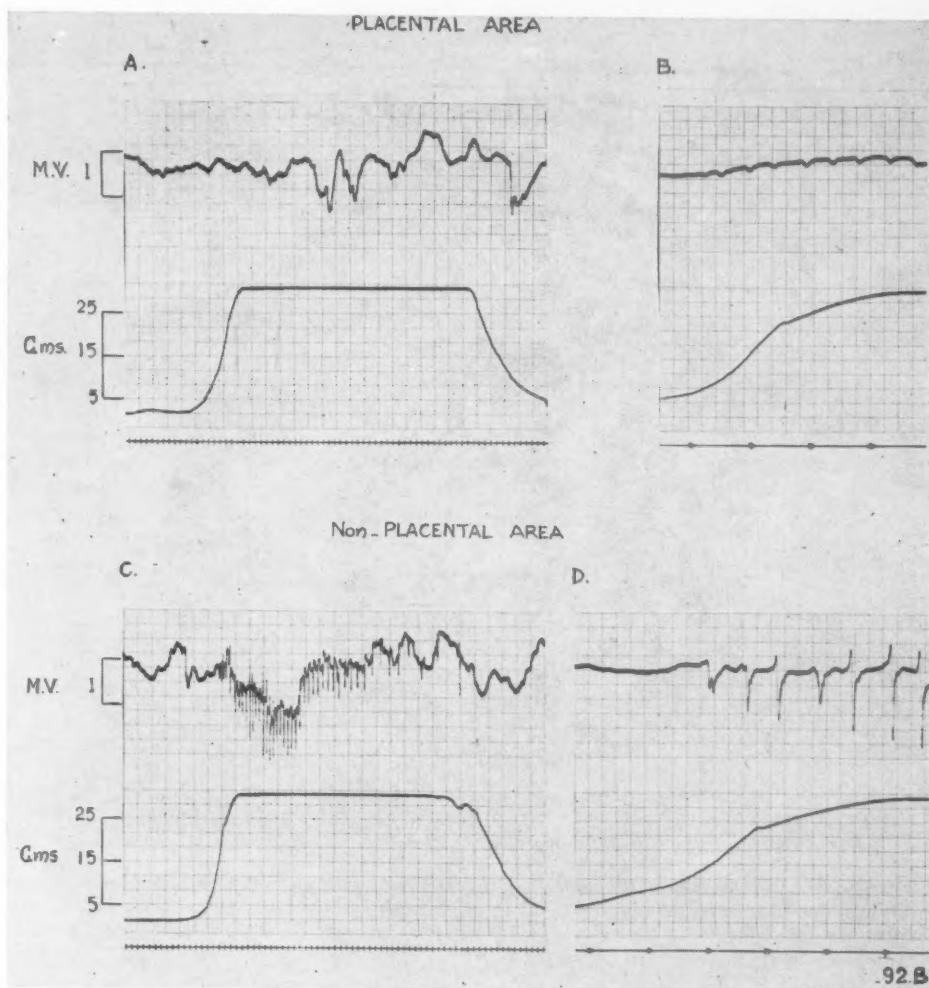


Fig. 2. Records from placental and nonplacental myometrium during contractions induced *in vitro* by continuous stretch. *A* and *B* records from a longitudinal strip of uterus from a pregnant cat before term. This strip was composed half of myometrium which had been lying over the placenta and half of myometrium which was contiguous but had not been lying over the placenta. *A* and *C* are slow and fast records from the former half. The records show: top line, the electrical activity recorded with a glass pore electrode; middle line, the isometric tension; bottom line, a time marker every second. The fluctuations in the slow electric record were shifts in the base-line due to the chemical potential at the electrode which occurred unrelated to uterine activity. Note that during a contraction only insignificant fast action potentials occurred. *C* and *D*, Similar records from an area a few millimeters away over a nonplacental area. Action potentials occurred during the phase of rapid tension increase and persisted until the onset of relaxation. Other records suggested that the action potentials were initiated at the extremity of the nonplacental myometrium, traveled to the junction of placental and nonplacental myometrium, and there died out.

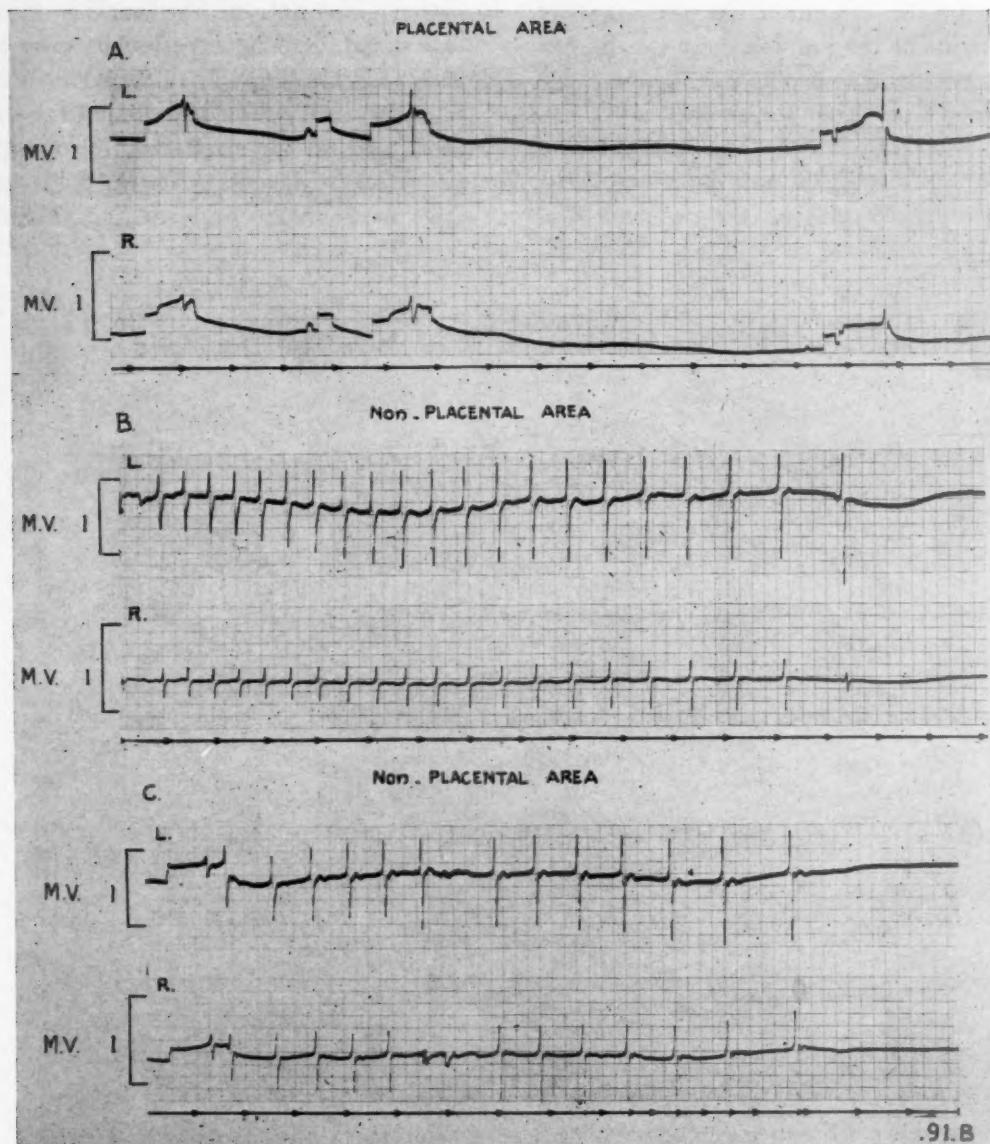


Fig. 3. Records of electrical activity at two electrodes 0.5 cm. apart placed with either over placental or nonplacental myometrium of the same strip as in Fig. 2. In these records, electrical activity was initiated by an additional sudden stretch superimposed upon a continuous stretch of 5 Gm. The beginning of this sudden stretch was signaled in the electrical records by a sudden upward shift and the end of stretch by a downward deflection. *A*, Record taken with both recording electrodes over the placental myometrium at the right. At the beginning of the record a single stretch initiated one action potential during the stretch. This potential was conducted from right to left. The action potential at the right electrode was distorted. The remainder of *A* shows two instances in which a single stretch was not sufficient to initiate electrical activity. A second stretch did initiate in each case a single action potential conducted from right to left. The relative inexcitability in these instances may have resulted from their occurrence during a contraction in the nonplacental portion of the strip. *B* and *C*, Two records of the activity induced by stretch at two electrodes over the nonplacental myometrium at the left. A tetanic burst of typical action potentials occurred in each case and lasted 12 to 14 seconds. They were conducted from left to right at a velocity of about 9 cm. per second. These and other records suggested strongly that the characteristic electrical activity of the nonplacental myometrium was not conducted to the placental area.

curred within 3 days. In the latter instances attempts were made to catch the animal in labor in the next day or two or to induce labor with Pitocin.

Records were not obtained during spontaneous labor because the animals proved capable of stopping labor if disturbed even after the birth of one or more fetuses. Records were taken in 2 animals during labor induced or restored by the injection of Pitocin.

In vitro studies. In a number of instances strips of cat and rabbit uterus were cut so that half the longitudinal muscle in the strip had originally been located over placenta

and the other half had not. These were suspended between muscle clamps for isometric recording and were stretched until a tension of 4 to 5 Gm. was maintained, as previously described.⁷⁻⁹ Electrical activity of the two portions of the longitudinal muscle was recorded by means of pore electrodes as previously described⁷⁻⁹ during both spontaneous contractions and those induced by additional stretch.

Chemical analyses of uterine wall. Various portions of the uterine wall were collected from other animals after different periods of pregnancy. The duration of gestation was assessed by measuring the rump-crown

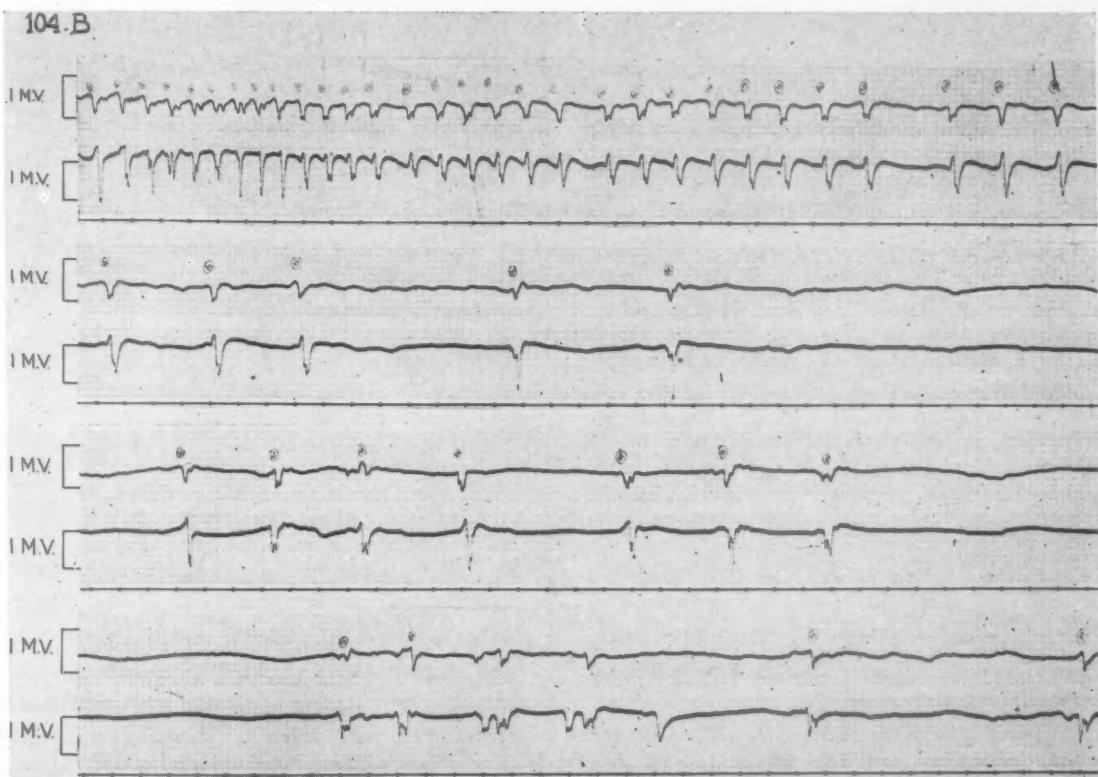


Fig. 4. A continuous record of conduction of action potentials in the pregnant cat uterus at term. The top electrode was located between the 2 fetuses nearest the ovary in one horn of a uterus. The bottom electrode was located 2.5 cm. away over the placenta of the fetus nearest the ovary. The arrival of activation was probably coincident with the beginning of the negative (downward) deflection of each action potential. Measuring from this point in the recordings from both electrodes, it was apparent that activity started in the top electrode and spread at a velocity of 9 cm. per second toward the bottom electrode throughout much of this record. Action potentials became irregular and infrequent as the burst persisted. Conduction occurred at a similar velocity but in a reversed direction during the last two action potentials in the bottom record. The variation in amplitude and configuration of action potentials in this record should be compared to the variation in vitro illustrated in Figs. 2 and 3.

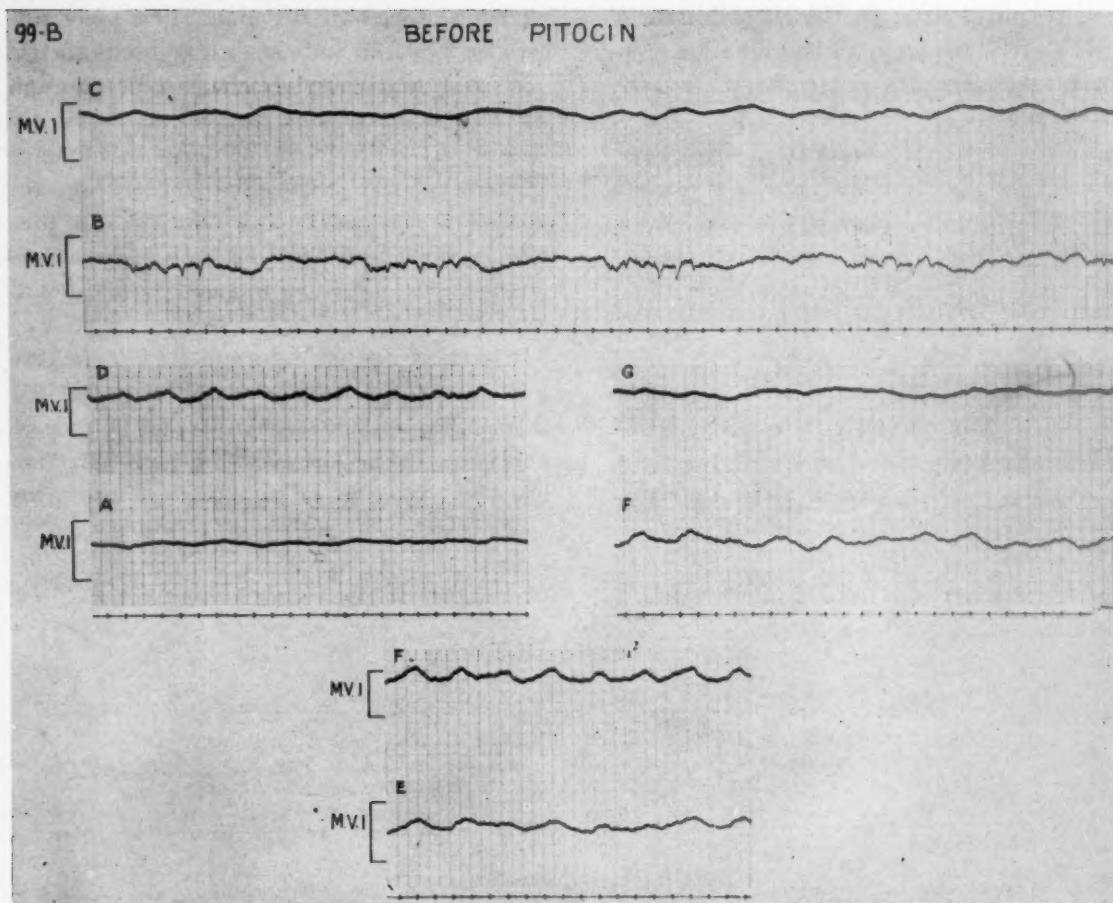


Fig. 5. Sample records of the electrical activity of the unstimulated cat uterus before term. (See Fig. 1 for positions of the electrodes.) There were no fast action potentials in any records except possibly those from electrode B. In the record from this electrode occasional fast action potentials may have occurred. Most of the slow fluctuations were attributable to fluctuations at the common ground electrode, since they tended to occur in both of the records taken simultaneously.

length of the fetuses and by the stage of fetal development (presence or absence of hair, etc.). The uterine wall segments were weighed immediately in some cases, while in others the endometrium was removed before weighing. Analytical procedures for water, sodium, chloride, and potassium concentrations in those tissues have been previously described.⁷⁻⁹

Results

In vitro studies. Electrical activity was recorded from strips of cat uterus derived in part from tissue previously located over the placenta. In strips from nonplacental areas it consisted of a tetanic burst of action po-

tentials.⁷⁻⁹ Occasionally in these experiments little or no electrical activity could be recorded from that portion of the longitudinal muscle previously located over the placenta during contractions induced by continuous stretch (Fig. 2). Even when such strips were stimulated by a sudden additional stretch, only one or two action potentials could be recorded during the subsequent contraction from the "placental" area while repetitive activity occurred over the rest of the tissue (Fig. 3). In some experiments using myometrium entirely derived from that overlying the placenta, the response to continuous or additional stretch was diminished. Such results were not, however, always obtained and

in other instances the differences in electrical activity between placental and nonplacental areas were less striking. In all of these strips however, action potentials were initiated in the nonplacental portions and appeared in the placental portion several seconds later. Similar results were obtained in a few experiments with strips of pregnant rabbit uterus. It seemed possible that the difference between "placental" and "nonpla-

cental" uterine muscle was diminished *in vitro* because of the absence of a continuous supply of progesterone.

In vivo studies.

Electrical activity in vivo. The electrodes used for recording *in vivo* were larger than those used *in vitro* (1 mm. versus 0.2 mm. in diameter) and were of a different type. There were consequent differences in the configuration of the action potentials. In

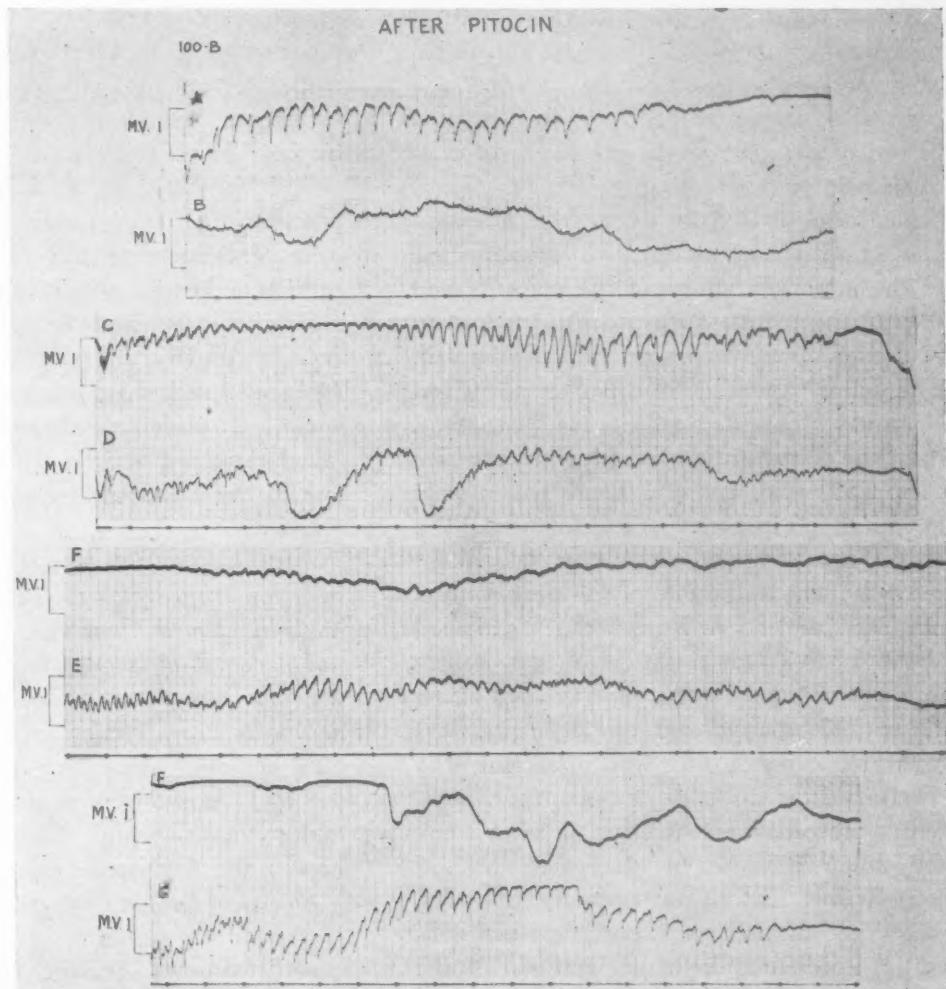


Fig. 6. Sample records of the electrical activity of the cat uterus before term but after stimulation by 0.1 unit of Pitocin intramuscularly. Same experiment as depicted in Fig. 5. Fast action potentials occurred at all electrodes except those over the placenta, B and F. There may have been some activity at placental electrodes (see F in record next to bottom one). However, this was clearly insignificant compared to the simultaneous activity at nearby nonplacental electrodes. Bursts of action potentials lasted less than 30 seconds in this experiment. Similar results were obtained 4 days later when 0.25 unit of Pitocin was injected. Initially there was activity at all but B electrode but it was of shorter duration at F, a placental electrode, and disappeared at this electrode sooner than at nonplacental electrodes.

vitro, action potentials consisted of an initial positive deflection followed by a larger and faster negative deflection and then by recovery. The initial positive deflections were about one-third the amplitude of the large negative deflections which averaged 1.0 mv. in peak-to-peak amplitude and 25 msec. in peak-to-peak duration. They were conducted at a velocity of 8 to 12 cm. per second and appeared at intervals as short as 150 to 200 msec.⁷⁻⁹ most of the action potentials at a given recording site were of relatively uniform amplitude (Figs. 2 and 3). Nothing has been noted in such records incompatible with the hypothesis that these are conducted all-or-none responses.⁷⁻⁹

In vivo, the electrodes were not arranged in order to facilitate the recording of conducted action potentials, but rather to permit comparison of activity at nearby placental and nonplacental sites. As a consequence, of the inhibitory effects of the placenta and the arrangement of electrodes, conduction of action potentials was rarely observed. The action potentials recorded at any given electrode showed quantitative variations from the configuration recorded in vitro (see Figs. 2, 3, 4, 6, and 8). There was usually an initial positive deflection, followed by a larger negative deflection with subsequent recovery. The amplitude of the peak-to-peak negative deflection varied but averaged about 1 mv. The duration of this deflection was definitely longer than in vitro (from 40 to 250 msec.), and the deflection was often not smooth but was interrupted by reversal of the direction of potential change. Similar records were observed in vitro when too much pressure by the electrode had altered the underlying myometrium. The magnitude of the initial positive wave generally represented a smaller fraction of the peak-to-peak deflection. The minimum interval between action potentials was about 300 msec., about double the minimum measured from in vitro records. The amplitude of the action potentials in a burst also varied more than in vitro but this may have been the result of variable shunting of the signals as the uterus contracted and changed

its anatomical relations to the other viscera and the body wall.

In the instances when conduction of individual action potentials occurred between two electrodes in vivo, the velocity was very close to that in vitro, 9 to 10 cm. per second (Fig. 4). In the instance depicted in this illustration, activity was conducted from an electrode located between two fetuses proximally toward an electrode located over the placenta of the fetus nearest the ovary in an animal at term.

The differences between electrical activity recorded in vivo and that in vitro probably are explicable in terms of the larger electrode size, of the variable shunting of the signals, and of the greater damage caused by these metal electrodes.

Electrical activity at placental and non-placental sites before term.

SPONTANEOUS ACTIVITY. There was very little spontaneous activity in the 11 experiments run on animals before term. In 2 surveys of activity all nonplacental electrodes (4 in all) picked up some electrical activity while all placental electrodes (4 in all) failed to record activity. In one such survey, one of the 4 placental electrodes picked up activity.

PITOCIN-INDUCED ACTIVITY. Intramuscular injection from 0.025 to 0.25 unit of Pitocin induced electrical activity under nearly all nonplacental electrodes before term. There was only one instance out of 14 possibilities in which Pitocin injection failed to induce such activity. There was only one instance out of 11 possibilities in which myometrium under the placental electrodes responded. Figs. 5 and 6 illustrate these findings.

Electrical activity at placental and non-placental sites at term.

SPONTANEOUS ACTIVITY. In studies of electrical activity at 18 electrodes implanted over the placenta, action potentials were recorded 5 times while 6 nonplacental electrodes recorded activity out of 25 studied. The instances of spontaneous activity were in one animal which was in labor and in which delivery occurred during the recording. In this animal, spontaneous electrical

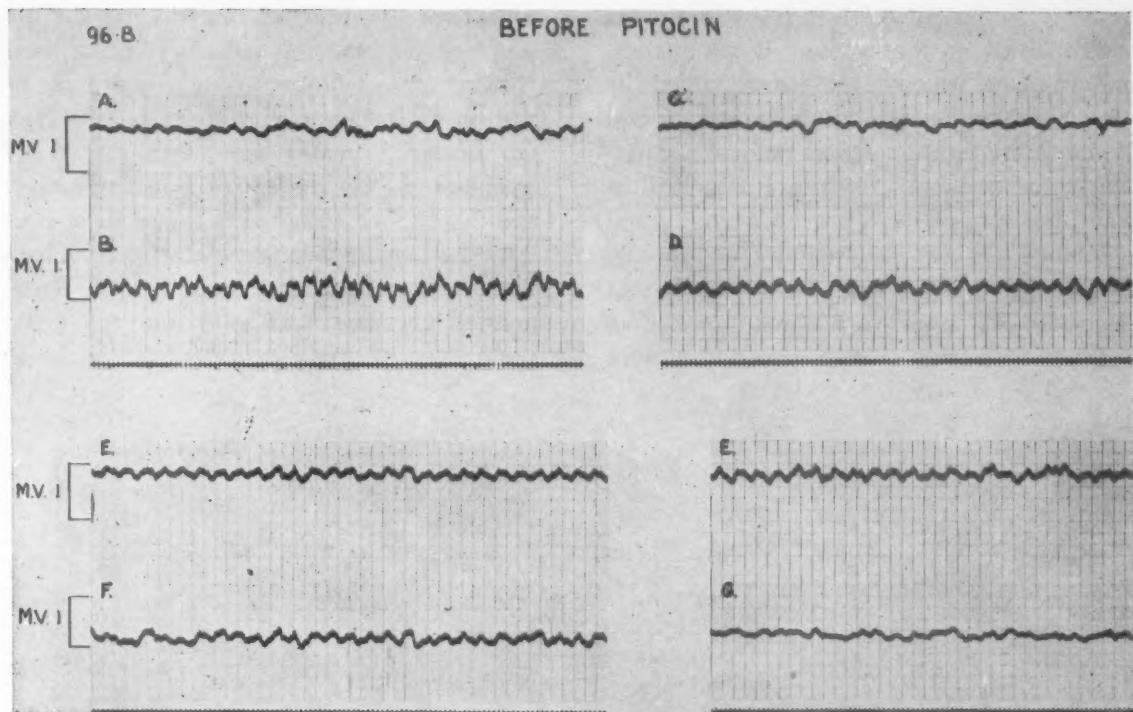


Fig. 7. Sample records of the resting electrical activity in the uterus of the animal as in Figs. 5 and 6 which were obtained 8 days later, at term. As before, there were no fast action potentials in the unstimulated uterus despite the fact that the animals were at or near term. Note the very slow paper speed used in these records, as indicated by the marks at one second intervals on the bottom of each record. The fluctuations in the electrical records resulted from the ECG and junction potential variations at the ground and muscle electrodes, chiefly the former.

activity occurred at both placental and non-placental electrodes.

PITOCIN-INDUCED ACTIVITY. After injection of Pitocin, activity was recorded at 14 of 16 placental sites, while it was recorded at all but one of 23 nonplacental electrodes. The instances in which electrical activity failed to occur were all in one animal which was delivered 3 days later and may have been not quite at term. Figs. 7 and 8 are from the same animal as Figs. 5 and 6 but 8 days later at term. This animal was delivered spontaneously within 24 hours after these records were taken. They illustrate the differences in response to Pitocin before and at term.

Electrical activity during delivery. Most of the records taken during expulsion of the fetus into the vagina were from electrodes at the placental site nearest the cervix (over the fetus about to be delivered) and at the

cervix itself. During one such continuous recording during expulsion of the fetus, the onset of electrical activity occurred first nearly simultaneously at these 2 electrodes, with the placental electrode preceding the cervical electrode by about 2 seconds. Thereafter, a series of bursts of action potentials occurred only at the placental electrode and not at the cervical one. This presumably corresponded with the movement of the fetus into the cervix. Thereafter, there were 4 bursts of action potentials which occurred as before at both electrodes with the placental electrode slightly ahead. Then there was a series of action potential bursts which occurred only at the cervical electrode. Presumably, they accompanied expulsion of the fetus into the vagina. Electrical inactivity for 10 minutes followed this phase of the delivery process. When activity recurred only the cervix was electrically active and

bursts of action potentials in this region were accompanied by contractions of the abdominal muscles which were accompanied by very rapid action potentials at the ground electrode in the abdominal wall. This pattern continued until birth.^{10, 11} Fig. 9 illustrates the stages of this process.

Control of electrical activity before and during delivery. Records from the various electrodes before delivery were examined in order to determine if there was any pattern

of spread of electrical activity. In the absence of simultaneous records from all electrodes, only tentative conclusions can be drawn. Electrical activity in response to Pitocin occurred nearby simultaneously at all nonplacental electrodes with an interval of less than 5 seconds between the onset of electrical activity at the various electrodes. There was no consistent pattern of spread. Thus, neither the electrodes near the tubes nor those near the cervix were consistently ahead.

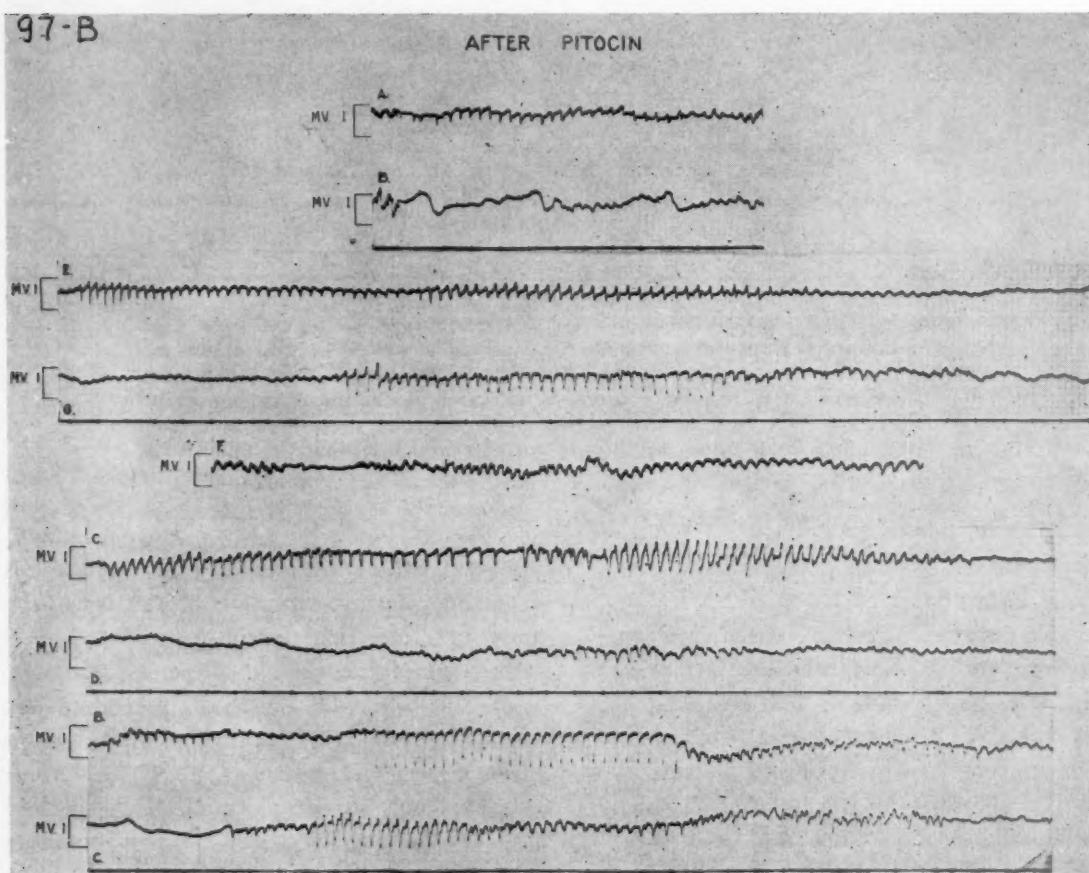


Fig. 8. Sample records of the electrical activity in the pregnant uterus of the cat during the same experiment as in Fig. 7, but after Pitocin, 0.1 unit. The top panel is a record taken after the injection of Pitocin of the activity at electrodes *A* and *B*. Electrical activity in *B*, a placental electrode, followed that in *A*. Comparison of this panel with the bottom two panels illustrates the fact that the fast activity usually spread toward the cervix from *A* to *B* to *C* to *D* in areas of the electrodes near the most distal fetus in the right horn. Several seconds intervened between the onset of activity at these several electrodes even though they were only 2 to 4 cm. apart. Obviously, the mechanism of spread in these instances was much slower than that in vitro (see Figs. 2 and 3), which had a velocity of 9 cm. per second. Both placental electrodes (*B* and *F*) were electrically active, although the action potentials of *F* were not large in this instance which was chosen for its proximity in time to the other records. Later on electrical activity at *F* became more marked while that at *G* died out. This record shows the general similarity of the configuration of action potentials in vivo to those in vitro. Most action potential bursts lasted 30 seconds or more.

Table I. Water and electrolytes in myometrium of pregnant cats—separate analyses of placental and nonplacental myometrium during pregnancy

Fetal length or status (cm.)	Tissue	No. samples	K	Na (mEq./kg. fresh weight)	Cl (mEq./kg. fresh weight)	H ₂ O (ml./kg. fresh weight)
0.7	Placental	1	54.0	105.3	90.5	824
	Nonplacental	1	49.3	97.8	113.9	828
4.5	Placental	3	58.5	109.6	112.3	788
	Nonplacental	3	48.2	104.3	97.8	815
6	Placental	3	80.0	110.4	100.5	801
	Nonplacental	3	63.7	107.5	100.7	820
7	Placental	3	65.6	98.5	93.8	798
	Nonplacental	3	71.4	109.6	108.1	811
7.5	Placental	3	74.8	94.0	99.3	797
	Nonplacental	3	67.3	110.7	111.7	807
7.8	Placental	3	51.9	97.2	90.1	823
	Nonplacental	3	50.8	101.9	84.0	836
8.2	Placental	3	56.8	90.7	104.5	783
	Nonplacental	3	70.9	92.6	92.2	792
11	Placental	3	78.5	74.6	69.2	814
	Nonplacental	3	82.0	87.3	65.2	823
12	Placental	5	62.0	79.6	76.3	815
	Nonplacental	5	± 3.3	± 4.0	± 3.1	± 3
12.5	Placental	3	63.1	80.5	86.7	819
	Nonplacental	3	62.6	91.7	86.8	821
13	Placental	5	63.0	107.9	82.9	795
	Nonplacental	5	± 4.9	± 6.0	± 2.1	± 13
13*	Placental	3	74.2	95.3	77.7	778
	Nonplacental	4	± 2.0	± 0.6	± 7.8	± 11
Post partum (10 minutes)	Placental	3	68.8	90.2	78.2	816
	Nonplacental	3	± 2.9	± 0.7	± 6.5	± 4
Post partum (5 to 8 hours)	Placental	3	62.8	74.3	77.2	819
	Nonplacental	3	± 2.9	± 1.6	± 1.5	± 3
Post partum (10 minutes)	Placental	3	56.4	72.6	74.4	841
	Nonplacental	3	55.9	74.7	71.7	852
Post partum (5 to 8 hours)	Placental	3	63.2	80.5	86.7	819
	Nonplacental	3	62.6	91.7	86.8	821

*One fetus out of two already delivered.

Since there was a zone of inhibition over the placenta, electrical activity could not spread continuously or down the uterine horns and, indeed, there was no evidence suggesting that it did. In consequence, it is necessary to presume that some mechanism accounted for the nearly simultaneous onset of electrical activity at electrodes located at distant sites

in opposite horns. Jung¹⁹ has reported similar findings and has suggested a nervous mechanism for coordinating uterine activity.

As illustrated in Fig. 6, the bursts of electrical activity in early pregnancy tended to be short. In general, their duration was less than 30 seconds.

At term, or during delivery, electrical ac-

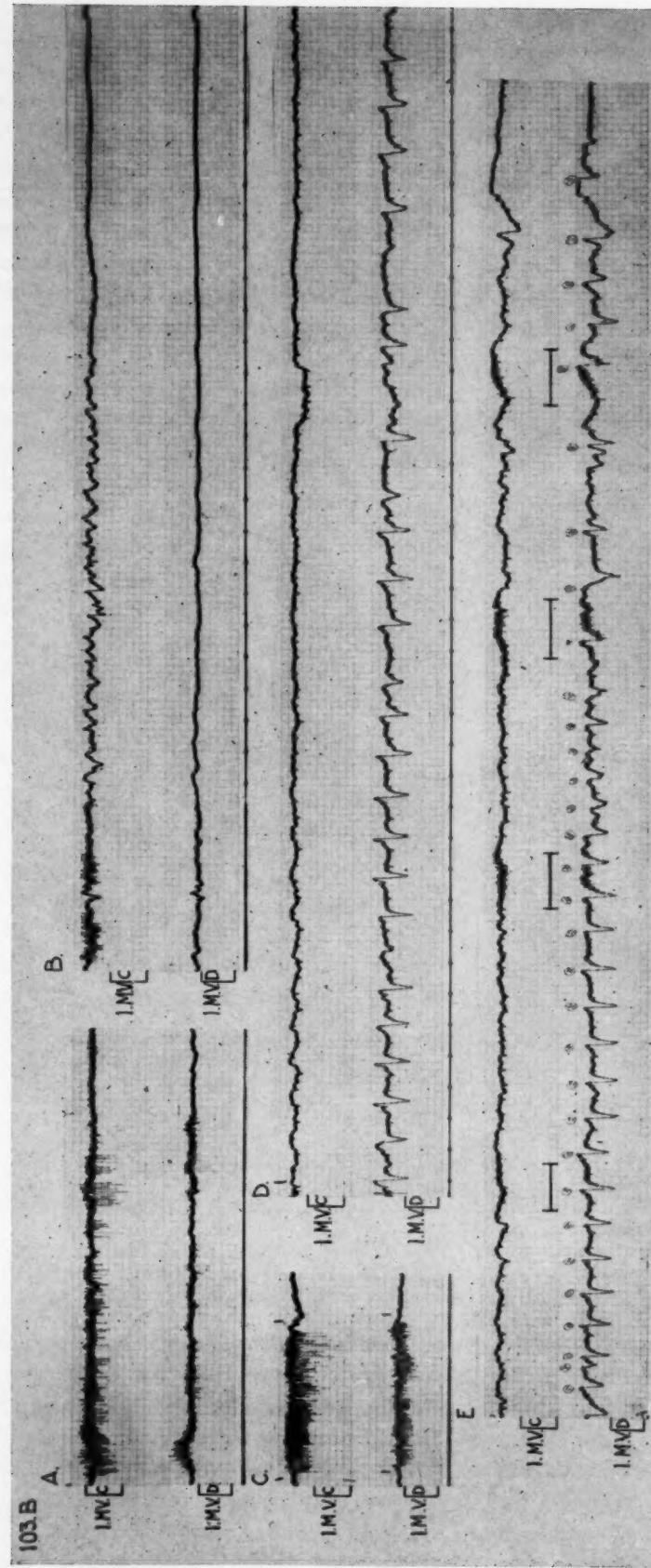


Fig. 9. Records of electrical activity from an electrode over the placenta of the fetus nearest the cervix in the right horn, *C*, and from an electrode in the cervix, *D*. These records were taken before and during delivery of this fetus. They followed the injection of Pitocin, 0.1 unit, by more than 30 minutes. Panel *A* shows the activity recorded before delivery of the fetus. Action potentials occurred at both electrodes, but were most consistent and largest at the placental electrode. Panel *B* is a record typical of several bursts which followed that in Panel *A*. There was virtually no activity in the cervical electrode, *D*. (Note the increase in paper speed about one quarter way through this panel and in Panels *D* and *E*. Presumably, such bursts occurred as the fetus was expelled from the uterine horn into the cervix. Thereafter, as illustrated by Panel *C*, there were short bursts of action potentials at both electrodes. After only 3 or 4 such bursts, the activity was again altered (Panel *D*) so that only the cervical electrode recorded action potentials. This type of activity continued until delivery. Just before delivery (Panel *E*) uterine contractions were aided by abdominal contractions. These were accompanied by repetitive fast electrical activity at both electrodes, which originated at the ground electrode on the abdomen. These were noted on the record by horizontal lines between vertical bars placed at the corresponding intervals between the 2 traces. Shortly after Panel *E*, delivery occurred.

tivity was usually initiated in the one nearest the Fallopian tubes of a pair of electrodes from which simultaneous records were taken. There were records which suggested that the placental electrode over the fetus nearest to the Fallopian tube was the area from which electrical activity was initiated.

Bursts of action potentials at term were much longer than prior to term. They lasted from 25 to 100 seconds and averaged nearly 60 seconds (Figs. 8 and 9).

Chemical ionic basis for differential sensitivity of placental and nonplacental electrodes. Previous studies from this laboratory have shown that progesterone treatment affects the chemical composition of the cat uterine muscle.^{12, 13} It diminishes its water, sodium, and chloride concentration and increases the potassium concentration expressed in terms of wet weight. Uterine muscle which had been overlying the placenta showed similar differences before term from myometrium from other areas (Table I). Similar differences have been reported in the electrolyte composition of the whole cat uterus after treatment with progesterone.¹² There was considerable variation in the ionic concentrations, but the data suggest that, as the fetus becomes large (7 to 12 cm.), the placental myometrium ceases to have an excess of potassium relative to nonplacental myometrium. This may be due to the action of large quantities of progesterone. However, in every instance, the water concentration in myometrium over the placenta was invariably

lower than in myometrium from other areas until the fetuses were at or near term (> 12 cm.). Near the time of delivery, differences in potassium distribution in the myometrium disappeared and this was usually also true of water concentrations. Table II shows that corresponding differences exist in the composition of the whole uterine wall when that overlying the placenta is compared to the remainder. Again, this distinction disappeared at term.

In rabbit uterus, progesterone has been shown to increase the rate of leakage of potassium from strips of uterus placed in potassium-free solutions and to diminish the increment in potassium loss induced by epinephrine.¹⁴ In Table III are summarized the results of an experiment with phosphate-free solutions illustrating that uterine wall from areas overlying the placenta shows the same difference from the rest of the uterine wall as that induced by progesterone. The rate of leakage of potassium is increased in the former pieces and the increment of loss in response to epinephrine is diminished. No experiments on rabbit uterus at term have been carried out.

Comment

Effect of placenta on uterine excitability. These results suggest there is at least a quantitative difference in the electrical excitability of cat (and rabbit) myometrium to Pitocin when this myometrium has overlain the placenta. Thus in most instances, before

Table II. Water and electrolytes in whole uterine wall of pregnant cats*

Stage of pregnancy	Origin of wall	No.	K	Na (mEq./kg. fresh weight)	Cl (mEq./kg. fresh weight)	H ₂ O (ml./kg. fresh weight)
Before term†	Over placenta	6	61.5 ± 2.5	98.2 ± 3.0	93.6 ± 2.1	813 ± 2.4
	Not over placenta	6	54.6 ± 3.8	97.8 ± 4.5	93.0 ± 3.0	826 ± 5.3
At or near term‡	Over placenta	6	57.5 ± 2.6	89.1 ± 6.6	90.0 ± 3.9	829.5 ± 4.9
	Not over placenta	6	62.6 ± 3.8	85.4 ± 8.0	84.2 ± 3.6	823 ± 4.6

*Variation of means expressed as standard errors.

†Fetal lengths 7 to 8.5 cm.; no fetal hair.

‡Fetal lengths 10 to 14 cm.; fetal hair present.

Table III. Rabbit uterine pieces: losses of potassium and phosphate during 15 minute exposure to phosphate-free media*

Origin of piece	Epinephrine (10 µg/ml.)	Losses into medium (mM./kg. fresh weight)	
		K	PO ₄ †
<i>Nonpregnant uterus</i>			
Estrogen	Absent	1.1 ± 0.24(12)	1.1 ± 0.07(12)
	Present	4.7 ± 0.53(4)	1.3 ± 0.09(4)
Estrogen plus progesterone	Absent	2.8 ± 0.32(12)	1.0 ± 0.05(8)
	Present	4.2 ± 0.46(4)	0.9 ± 0.05(4)
<i>Pregnant uterus</i>			
Not over placenta	Absent	0.7	1.2
	Present	5.8	1.5
Over placenta	Absent	2.1	1.1
	Present	1.3	1.1

*Variation of means expressed as standard errors.

†Phosphate determined by method of Fiske and SubbaRow.¹⁸

term, such areas of myometrium responded poorly compared with other areas to Pitocin injection and in many cases did not respond at all. Similarly, uterine strips studied in vitro containing half placental and half nonplacental myometrium sometimes showed similar differences in sensitivity to stretch or in electrical activity during contractions induced by stretch. Thus, continuous stretch or additional sudden stretch caused contractions but there was electrical activity only in the nonplacental myometrium.

This difference might become a qualitative one if a system of recording *in vivo* would be devised which was sufficiently non-irritating. It may be that, in those instances in which action potentials were recorded from placental myometrium before term, the electrode itself had been forced into position so that it was acting as an additional stimulus.

At term, no distinction between the excitability of placental and nonplacental myometrium could be discerned. In fact, electrical activity at the placental electrodes more often than not preceded and outlasted activity at other electrodes. This might not be surprising because of the greater distending force exerted by the fetus.

Mechanism of the placental effect on excitability. Determinations of the electrolyte

and water composition of the cat myometrium and of the cat uterine wall indicated that similar differences were present before term in areas over the placenta as were induced by progesterone in nonpregnant animals.^{12, 13} Thus, the water sodium and chloride concentrations were diminished and the potassium concentrations were elevated. These differences disappeared at term.

Similarly, the leakage of potassium from the rabbit uterus, both with and without epinephrine, is altered by progesterone pre-treatment.¹⁴ Similar differences were noted in potassium leakage in rabbit uterus which had been in contact with the placenta when this was compared to leakage from nonplacental pieces. Therefore, all the chemical properties of these pieces suggest that they differ as a result of the action of progesterone.

These results are compatible with the proposal recently made by Csapo^{2, 3} that the placenta produces progesterone which acts locally on the overlying myometrium to alter its properties. These properties seem to be its ion and water distribution and its electrical excitability in response to stretch and to Pitocin. As a consequence of the band of diminished excitability around each fetus, peristaltic, propulsive electrical activity is prevented until term. The greater excita-

bility of the nonplacental myometrium would also serve to prevent propulsive movements of the fetuses since such movements would stretch and induce contractions in these relatively excitable areas. Such contractions would tend to force the fetus back to its original position.

At term, the band of excitability around the fetus disappears and propulsive activity becomes possible. What actually induces labor is unknown, but a variety of evidence points to the possibility that it may be in response to circulating oxytocin. It has been shown that endogenous or exogenous oxytocin is capable of inducing labor in the rabbit,^{10, 15} and that at term the uterus of rabbits and of human beings becomes able to respond by propulsion to much smaller doses of oxytocin.^{4, 5} The results of this study clearly show that the placental myometrium at term becomes capable of electrical excitation by oxytocin and this supports the proposal that oxytocin is the excitant of labor. Whether or not similar evidence can be found for human beings will depend upon analysis of the electrical activity of the human uterus in areas over the placenta and elsewhere before term, at term, and during labor. It has been shown recently in this laboratory¹⁶ that the electrical activity of the human uterus *in vitro* is not different from that of other species. In addition, if placental effects are found, it will be necessary to determine whether they could result from the action of progesterone on the myometrium. Studies of the excretion of progesterone or of progesterone metabolites or even of blood levels of these steroids appear to provide no critical indication on the local action of progesterone on the adjacent myometrium.

In addition to its inhibitory actions, progesterone alters the properties of the myometrium in other ways. It results in prolonged tetanic bursts of action potentials⁹ which may enable the uterus to provide the prolonged force necessary for gradual dilation of the constrictions blocking fetal expulsion.

As yet, the cellular mechanisms whereby

progesterone alters the properties of the myometrium are unknown. These mechanisms do not appear to involve primarily depletion of cellular potassium^{12-14, 16} as postulated by Csapo.³ They may involve some aspect of sodium transfer across the cell membrane as recently postulated by Jung.¹⁷

Summary

1. The electrical activity of the pregnant cat uterus consists of repetitive action potentials which appear to be conducted and to initiate a prolonged contraction.
2. *In vitro*, myometrium which had been over the placenta was less excitable by stretch. Action potentials fail to occur in these areas or spread to placental myometrium only secondarily.
3. *In vivo*, myometrium over the placenta showed little or no spontaneous activity before term and likewise usually failed to respond to intramuscular injections of Pitocin (0.025 to 0.25 units) which activated myometrium in other areas. At term, the distinction between the electrical excitability of placental and nonplacental myometrium disappeared.
4. The ionic composition and the ionic exchanges in placental myometrium differed from the composition and exchanges in other myometrium in a manner which suggested that placental myometrium was under the influence of progesterone.
5. These results were considered to support the hypothesis that the local inhibitory action of placental progesterone may be important in preventing abortion before term and that the withdrawal of that action may play a role in initiating labor.

Addendum. Since the submission of this manuscript for publication, Goto and Csapo (*J. Gen. Physiol.* 43: 455, 1959) have published evidence which is consistent with that reported here and which has led them to modify Csapo's earlier theories.^{2, 3}

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Ceroid in the placenta

With special reference to meconium staining thereof

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DURING routine examination of the placenta, many yellow globular pigments were noted in macrophages in the mesenchymal layer of the amniotic membrane and choriocytic plate of meconium-stained placentas. The pigments resembled hemosiderin or bile pigments; they were, however, proved to be ceroid and related lipopigments. Upon further study the pigments were also found in the trophoblastic shell and decidua of the amniotic membrane showing advanced degeneration and necrosis.

Although ceroid had been found in various pathologic conditions in animals and humans, review of the literature failed to reveal any report of the presence of ceroid in the placenta. In this paper the incidence of ceroid in the placenta is reported, and its nature, sources, and mode of formation are discussed.

History, characteristics, nature, and mode of formation

Ceroid is a yellow, globular, lipoid pigment, which was first discovered in cirrhotic livers of rats fed diets deficient in lipotropic factors, almost simultaneously by four groups of investigators.^{1, 11, 21, 35} It was repeatedly noted in their subsequent series of experiments and also by other investiga-

tors.^{2, 4, 10, 12-14, 23, 24, 36, 37, 55} The term "ceroid" was given by Lillie and associates³⁶ in 1942 to this pigment because of its wax-like character.

On sections stained with hematoxylin and eosin it appears as a yellow globular pigment ranging from 1 to 2 μ in diameter. Its histochemical properties were extensively studied by Endicott and Lillie¹⁵ and by Lee.³⁸ The distinctive properties of ceroid on sections include (a) golden yellow color when unstained, (b) PAS-positivity, (c) strong acid-fastness, (d) insolubility in xylol or other organic fat solvents, (e) affinity for fat stains such as Sudan IV or oil red O on both frozen and paraffin sections, (f) strong basophilia, and (g) negativity for iron or bile pigment stainings. In sharp contradistinction to lipofuscin, it gives negative reaction to Schmorl's stain.¹⁵ It gives a characteristic stable bright yellow to golden brown or greenish yellow fluorescence under ultraviolet ray microscopy, on both frozen and paraffin sections,^{15, 36, 42, 50, 51} but not in xylol or xylol clarites.¹⁵ György considers the pyronin-methyl green stain to be a sensitive method of demonstrating the pigment.²² Popper, György, and Goldblatt reported methyl green stain to be the most reliable.⁵⁰

In less than two decades after the original reports, ceroid was found to be widely distributed in the animal kingdom. In rats with experimental cirrhosis of the liver due to deficiency of the lipotropic factor, ceroid was discovered, not only in the liver, but also in various organs; e.g., in the spleen, lymph nodes, adrenal cortex, bone marrow,

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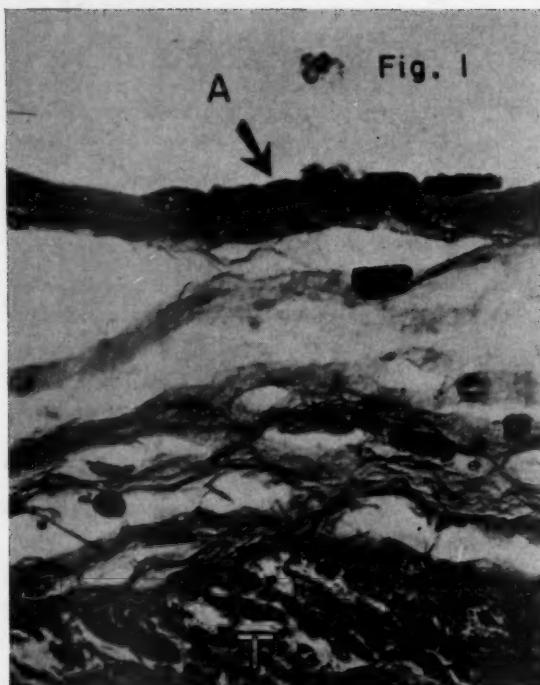


Fig. 1. Meconium-stained amniotic membrane. The amniotic cells (*A*) are heavily laden with phagocytized meconium and are undergoing necrosis. Several macrophages laden with yellow granular to globular pigments and fat droplets are present. Trophoblasts (*T*) show advanced degeneration and necrosis. (Hematoxylin and eosin. $\times 400$; reduced $\frac{1}{6}$.)

and lung.^{5, 36, 37} It was also found in vitamin E-deficient rats,^{6, 7, 23, 39-43, 54} in vitamin E-deficient guinea pigs,⁴⁴ in cirrhotic livers of mice following protracted carbon tetrachloride poisoning,^{12, 33} in mink,¹⁵ in swine,⁸ in fish,⁵⁶ and in many other animals. It was also found in various parts of humans; e.g., in smooth and skeletal muscles, phagocytes, liver cells, brain, pars nervosa of hypophysis^{45, 46} and ovary.⁵¹ Of particular interest is the presence of brown pigment, which is indistinguishable from ceroid both on staining characteristics and on fluorescence, in various parts of the sexual organs of animals and humans; e.g., in smooth muscle cells of vagina, uterus, and seminal vesicles of rats fed vitamin E-deficient diets^{39, 40, 42, 43, 54}; in testes of vitamin E-deficient guinea pigs⁴⁴; in ovaries and testes of vitamin E-deficient rats³⁹; in regressing corpus luteum of rhesus monkeys (*Macaca mulatta*)⁵³; and in hu-

man ovaries, where it was first thought to be "wear and tear" pigment.⁵¹

The exact nature and mode of formation of ceroid and its relation to lipofuscin and hemofuscin remain to be elucidated. Blumberg and Grady² regarded ceroid as hemofuscin. Hemofuscin is an iron-free yellow granular pigment first reported by von Recklinghausen⁵² and characterized further by Hueck³² and by Mallory, Parker, and Nye.³⁸ Endicott and Lillie,¹⁵ however, pointed out the difference in the appearance, location, and staining between ceroid and hemofuscin. Pearse⁴⁷ is inclined to regard hemofuscin to be similar to lipofuscin. He⁴⁷ and Lillie³⁴ classified ceroid as one of lipofuscins. It is generally believed that all of them are derived, mainly or partly, from lipids.

Ceroid is believed to be derived from unsaturated lipids through a train of reactions—autoxidation, peroxide formation at double bonds, and polymerization.^{3, 7, 13, 27, 29, 31} This process is exaggerated and results in pathologic accumulation of ceroid or ceroid-like pigments in tissues in the case of absolute or relative deficiencies of biologic antioxidants such as vitamin E.⁸ The formation of ceroid is, furthermore, prevented by the administration of vitamin E.^{23, 41, 51} Ceroid is thus an autoxidation product of unsaturated lipids and represents a typical lipofuscin in an early stage of oxidation.⁴⁷

Mason and Emmel^{39, 40} regard it to be an unusually stable lipoid-protein-pigment combination. Edwards and Dalton¹² consider it to be a conjugated lipoid. György and Goldblatt²¹ postulate ceroid to be "lipoidal material in some form of intimate combination with the protein which interferes with its removal by lipoid solvents," thus giving positive reactions for Sudan IV, oil red O, and other fat stains even on paraffin sections. With further oxidation, it loses its affinity for fat stains and becomes a typical lipofuscin and perhaps "wear-and-tear pigment."

Material and method

Out of 203 consecutive placentas delivered from the mothers belonging to the Child Development Study sponsored by the National

Institutes of Health, all but 3 placentas were examined. The 3 placentas excluded from the study consisted of one placenta from a set of identical twins and 2 from a set of fraternal twins. The placentas weighed between 350 and 700 grams. Placentas were kept in a refrigerator. Once a week, one or more long strips of the amniotic membrane, at least 2 perpendicular sections of the entire thickness of a placenta, and two sections of the umbilical cord were cut and fixed in 10 per cent formalin buffered with 2 per cent sodium acetate. In addition to the routine hematoxylin and eosin stain, all the cases containing macrophages laden with yellow granular to globular pigments were subjected to methyl green,⁵⁴ oil red O, periodic acid-Schiff, and Ziehl-Neelsen's acid-fast stains. Many sections were, in addition, subjected to Sudan IV, Schmorl's, and Gomori's iron stains, as well as the oxidation by Gmelin's and Stein's reagents and hydrogen peroxide for bile pigments. The majority of the cases were examined under the ultraviolet ray microscope for fluorescence. A few frozen sections of the amniotic membrane and chorionic plate were stained with oil red O; this was rarely used, however, because of technical difficulties.

The diagnosis of ceroid was made when the pigments demonstrated all the characteristics of ceroid. Pigments which did not satisfy all the characteristics were classified as ceroidlike pigments.

Results

In meconium-stained placentas many amniotic cells, mesenchymal cells and macrophages of the amniotic membrane contain droplets and vacuoles of fat. An apparent transformation from fat droplets and vacuoles to diffuse and granular yellow pigments and thence to globular yellow pigments can be histologically recognizable. In macrophages laden with droplets and vacuoles of fat, a small quantity of diffuse to granular yellow pigments appear and gradually increase in amount (Fig. 1); finally, the cytoplasm of the macrophages becomes laden with yellow diffuse to granular pigments.

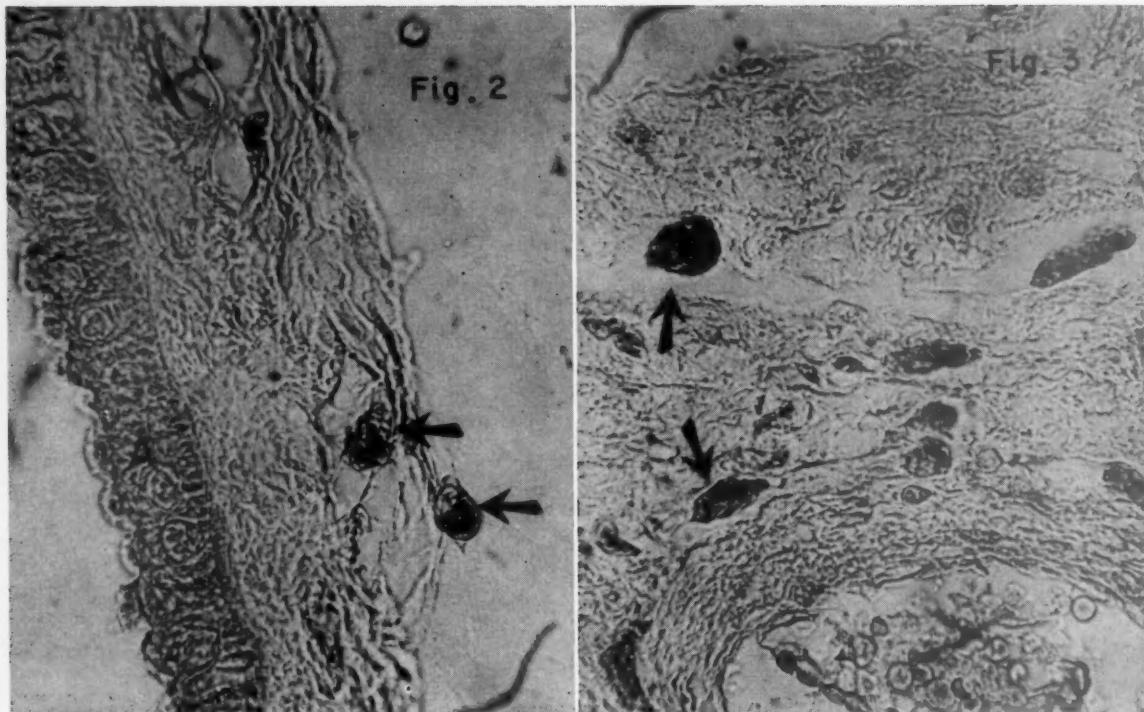
Later, in addition, globular yellow pigments appear and increase in number. Eventually, mesenchymal cells and macrophages contain many globular pigments (Figs. 2, 3, and 4). Staining characteristics of these pigments are shown in Table I. Typical staining and fluorescent characteristics of ceroid are, however, shown only by a part of the globules, while a large proportion of the pigments either remain unstained or show characteristic reactions of ceroid only to a part of the stains (Table II); hence, the latter pigments were classified as ceroidlike pigments.

Table I. Results of histochemical and fluorescence studies on the yellow globular pigments in the placenta (on paraffin sections)

Histochemical reactions	Results
Hematoxylin and eosin stain	Yellow to brownish yellow
Periodic acid-Schiff stain	+
Acid-fast stain (Ziehl-Neelsen)	+
Fat stains (oil red O, Sudan IV)	+
Methyl green stain	Violet
Schmorl's reaction	-
Reactions for bile pigments	
Stein's stain	-
Gmelin's reaction	-
H ₂ O ₂ oxidation	-
Feulgen's reaction	Occasionally +
Gomori's stain for iron pigments	-
Ultraviolet ray microscopy	Greenish yellow fluorescence on unstained paraffin sections, but not on xylol clarites

Table II. Relation between the degrees of meconium staining of the placentas and incidence of ceroid

Degrees of gross meconium staining	No. of gross meconium staining	Incidences of ceroid
+	32	7 (22%)
++	15	6 (40%)
+++	22	10 (45%)
Total	69	23 (33%)



Figs. 2 and 3. Details of ceroid in macrophages in the amniotic membrane. Sections were stained with methyl green. The transformation of slender elongated mesenchymal cells to oval cells and then to typical plump round macrophages is evident. They contain violet-colored globules of ceroid ranging from a few to several in number (arrows). A, amniotic cells. ($\times 600$; reduced $\frac{1}{2}$.)

The ceroidlike pigments usually demonstrate intense affinity to fat stains but show barely or weakly positive reactions to PAS and acid-fast stains, and also faint basophilia. They also fail to emit fluorescence. They are presumed to be lipopigments in a preceroid stage of oxidation.

The incidences of gross meconium staining and ceroid of the placenta and their relationship are summarized in Table II. Whenever faint greenish tint of the amniotic membrane is noted, the case is included in the 1-plus group. Of the 200 placentas examined, 69, or 35 per cent, showed gross meconium staining. Of the latter, 23, or 33 per cent, were found to contain ceroid in macrophages and mesenchymal cells. Furthermore, in addition to ceroid, all of them contained ceroidlike pigments. Eleven more meconium-stained placentas contained only ceroidlike pigments (Table II). In 44 (64 per cent) of the 69 meconium-stained pla-

centas, meconium was found to have been phagocytized by amniotic cells; these cells were seen to be in various degrees of degeneration. In extreme cases, large areas of the membrane were denuded of lining amniotic cells (Fig. 1), in many of which meconium was found to be phagocytized by macrophages. The phagocytized meconium can be readily differentiated from ceroid by morphologic and staining characteristics even on sections stained with hematoxylin and eosin. Meconium, furthermore, does not emit fluorescence when exposed to ultraviolet rays.

In addition to the above location, ceroid is also found in the trophoblastic shell and decidua of the amniotic membrane, when they show advanced degeneration and necrosis; i.e., it is found in amorphous eosinophilic necrotic debris of tissues and blood and in trophoblastic and decidual cells showing fatty degeneration (Fig. 5). As is

the case with ceroid associated with meconium staining, typical morphologic, staining, and fluorescent characteristics are shown only by a part of the pigments, and the remainder of them are presumed to be still in the preceroid stage of the oxidation. Many fragments of red blood cells are discernible in necrotic debris. The incidence of ceroid in this location has no correlation with the meconium staining of the placenta, but is apparently related to the degree of tissue necrosis.

Comment

It is now evident that some substances contained in the meconium or formed by its mixture with vernix caseosa perfuse into the amniotic membrane, are phagocytized by macrophages and mesenchymal cells, and are converted to lipopigment (ceroid and ceroidlike pigments or lipofuscin) from the fact that ceroid in the macrophages of the membrane is seen only when it is stained with meconium (Table II), and, with a few exceptions, the presence of macrophages laden with lipofuscin is likewise associated with meconium-staining of the membrane.

On the other hand, pathogenesis observed histologically, as well as the lack of correlation with the incidence of meconium-staining of the placenta or of ceroid in macrophages, and its close association with the degree of the necrosis suggest that ceroid in the trophoblastic shell and decidua of the amniotic membrane is most likely formed from certain precursors in loco rather than from those in the meconium. Previous investigators are in agreement that unsaturated lipids are the most likely precursors of ceroid. The only other possible precursor reported is bilirubin.⁴³

1. Unsaturated lipids as precursors. From the numerous reports quoted previously and from this observation, it can be assumed that unsaturated lipids in the meconium and necrotic debris and those formed by the interaction between vernix caseosa and meconium can be converted to ceroid or related lipopigments by autoxidation, peroxide formation, and polymerization. In

fact, ceroid or ceroidlike pigments are formed from lipids high in content of unsaturated fatty acids and their esters in foci of aspiration pneumonia^{17-20, 48, 49} and in lipoid-aqueous interfaces of subcutaneously, intramuscularly, and intraperitoneally administered lipids.^{13, 27-31} In addition to the above foreign lipids, compounds amenable to the transformation are found to be present in mammalian liver, brain, and blood.³¹ Ceroidlike pigments were also formed in traumatic hemorrhagic fat necrosis of the omentum of rats and also in *in vitro* experiments.^{25, 26} Unsaturated lipids are converted to ceroid by means of *in vitro* oxidation.^{13, 25, 26} These yellow globular pigments derived from unsaturated lipids and also in vitamin E-deficient animals and humans are considered to be identical or very closely related to ceroid.^{3, 13, 25, 26, 39, 40, 46, 54}

The fact that, although normal amniotic fluid contains a small amount of lipids of vernix caseosa, no lipopigments are formed in the normal membrane might be due to its low content of unsaturated lipids. Furthermore, digestive enzymes of meconium

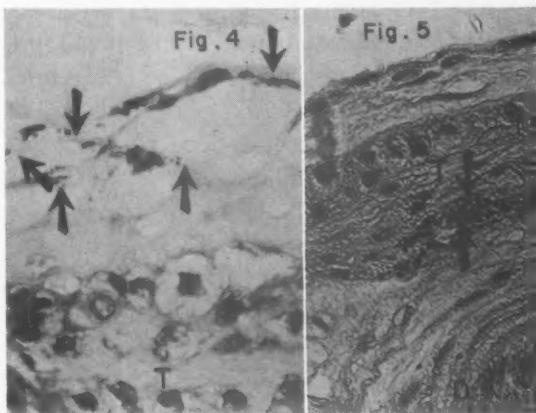


Fig. 4. Ziehl-Neelsen's acid-fast stain showing bright red ceroid globules (arrows) in macrophages and mesenchymal cells of the amniotic membrane. T, trophoblasts. ($\times 640$; reduced $\frac{1}{2}$.)

Fig. 5. Ceroid globules (arrows) in trophoblasts (T) and necrotic debris of the amniotic membrane. D, decidua. This paraffin section was stained with oil red O and ceroid globules are brilliantly orange red. ($\times 400$; reduced $\frac{1}{2}$.)

will accelerate the decomposition of vernix caseosa and result in the formation of abundant unsaturated lipids. This problem is now being investigated. The amniotic cells, furthermore, are damaged by meconium or conditions leading to its in utero discharge from the fetus, thus facilitating the perfusion of precursors into the membrane.

Ceroid found in the trophoblastic shell and decidua is probably derived in loco from unsaturated lipids in the necrotic debris. The importance of necrotic tissue and red blood cells for its formation is emphasized by Hartroft.^{25, 26} The rich vascularization and the presence of some liquefaction degeneration will be a predisposing factor for abundant accumulation of such necrotic debris and, in turn, the formation of ceroid here. The degeneration may be further exaggerated in cases of local anoxia.

Conditions present in meconium-stained placentas and in the amniotic membrane showing advanced necrosis indirectly support Casselman's theory that whenever unsaturated fatty acids accumulate in tissues to such an extent that a relative lack of biological antioxidants results, autoxidation of the fats and their conversion to ceroid are favored.³ It appears that imbibition of the amniotic membrane by meconium will import unsaturated fatty acids (exogenous lipids), and tissue breakdown by injurious effects of meconium, anoxia, bacterial infection and other physiologic disturbances will result in accumulation of toxic tissue breakdown products including unsaturated lipids (endogenous lipids). These toxic products will in turn exert detrimental effects upon the remaining tissues, thus setting up a vicious circle. In any dystocia or conditions leading to in utero discharge of meconium from the fetus, disturbances of normal physiology must certainly be present. Furthermore, the possibility of low-grade infection which may not be recognizable by the routine histologic examination cannot be ruled out, especially in such distressed conditions.

Since fresh placentas were examined

grossly and blocks were cut and fixed in formalin only once a week, many of them were kept in a fresh condition for nearly a week in a refrigerator. The autoxidation of precursors into ceroid probably continues even while the placentas are being kept in a refrigerator, for the process does not necessarily require living cells; indeed, the transformation of films of unsaturated lipids into ceroidlike pigments was noted upon exposure to the air, and this process is accelerated by oxidants.¹³

2. Bile pigments. The possibility that bilirubin is a precursor was referred to by Moore and Wang,⁴³ although they were skeptical about it. They reported the fluorescence of bilirubin after oxidation, which is, however, denied by Pearse⁴⁷ and Desmond and Lindley.⁹ At present this possibility is very remote.

Summary

1. The presence of ceroid, a yellow globular lipoid pigment, in the placenta is reported. Although ceroid has been found in various pathologic conditions in animals and humans, there has been no report of its occurrence in the placenta.

2. The nature, characteristics, and a possible mode of formation of ceroid are reviewed. It is thought to be derived from unsaturated lipids through the process of autoxidation, peroxide formation, and polymerization; it probably represents lipofuscin in an early stage of its oxidation.

3. Two types of ceroid are found in the placenta: (1) ceroid associated with meconium staining of the placenta and (2) ceroid associated with necrosis.

4. The former type of ceroid is present in macrophages and mesenchymal cells of the amniotic membrane and chorioamniotic plate of meconium-stained placentas. It is probably derived from unsaturated lipids either contained in the meconium or formed by the interaction of meconium and vernix caseosa. Unsaturated lipids then imbibe the amniotic membrane, are phagocytized by the mesenchymal cells and macrophages, and are converted into ceroid through autoxida-

tion. The macrophages are derived from mesenchymal cells of the membrane. The possibility that bilirubin is a precursor, although postulated by a few previous workers, is very remote.

5. The latter type of ceroid is seen in necrotic debris of tissues and blood and in trophoblastic or decidual cells undergoing fatty degeneration. It is probably formed, *in loco*, through autoxidation of unsaturated lipids in the debris. Necrotic tissues and red blood cells may play an important role in the formation of ceroid.^{25, 26}

6. Accumulation of unsaturated lipids in

the placenta from either exogenous (from meconium) or endogenous (from tissue breakdown) sources may result in the relative lack of biologic antioxidants, which, in turn, favors the formation of ceroid.

7. Of 200 placentas examined, 69, or 34.5 per cent, showed meconium staining of the membrane; of the 69 placentas, ceroid was found in macrophages and mesenchymal cells in 23, or 33 per cent.

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The management of eclampsia

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TOXEMIA of pregnancy has evolved into the foremost cause of maternal morbidity and mortality in the United States today.¹ This does not mean that the incidence or severity of toxemia has increased. Indeed, a rather significant reduction in the incidence of toxemia has occurred in many areas, but this has not kept pace with the reduction and control of the other major causes of maternal deaths, namely, hemorrhage and infection. The southeastern United States has been noted for its high incidence of toxemia, and this continues in spite of efforts to control the disease.

For several years much of our investigative effort has been directed toward a better understanding of the disturbed physiology in toxemia and toward more effective means of controlling this disturbance. The fact that our efforts in this regard have contributed little toward the prevention of toxemia is illustrated by a continuing incidence of 18 per cent of toxemia among current admissions to the obstetric service of the City of Memphis Hospitals. It is also of interest to note that 41 per cent of the 84 maternal deaths which have occurred during the past 10 years were directly related to toxemia. There is a continuing need for the education of physicians and patients to the importance of adequate prenatal care in the prevention of toxemia. In this modern age, most patients and some physicians are totally unaware of the real significance of

prenatal care. Prevention remains our most important weapon in the control of this disease.

This report is another on our experience with the clinical management of patients with eclampsia. In this series, several modifications in therapy have been introduced. An attempt has been made to correlate the results of these with results obtained with use of previous therapeutic regimens.^{2, 3}

Material

Between April 15, 1951, and Sept. 30, 1958, 220 patients with a diagnosis of eclampsia were managed in the Maternity Division of the City of Memphis Hospitals. Ninety-eight per cent of these were Negroes. One hundred ninety-nine of these patients were delivered of 214 babies. Nineteen were delivered prior to admission and 2 died undelivered.

The diagnosis of eclampsia was made by the presence of hypertension, edema, and/or albuminuria accompanied by convulsions. Other convulsive disorders were excluded. The average age of the patients in this group was 21 years. Twenty-six per cent were 16 years of age or less and 69 per cent were 21 or less. The average number of pregnancies per patient was 2.3; however, 62 per cent were primigravidae. Twenty-three per cent of the patients who had had previous pregnancies gave a history of having had toxemia, and 5.9 per cent had eclampsia previously. During the period of time in which 220 patients were observed with eclampsia there were 50,105 deliveries. The incidence, therefore, is 0.44 per cent.

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This represents a continued reduction from an incidence of 1.2 per cent between 1941 and 1945 and 0.75 per cent between 1945 and 1950. We believe that this reduction in incidence represents a greater acceptance of prenatal care; however, a glaring deficiency is seen when one considers that 65 per cent of the patients in this series had no visits either to the obstetrical clinic or to a private physician. Only an insignificant number had enough visits to be termed adequate prenatal care. As might be suspected, 62 per cent of the patients came from outlying areas not normally served for prenatal care by our clinic. We were unable to show a significant seasonal variation in the incidence of eclampsia.

Maternal mortality

There were 15 maternal deaths in this group of 220 patients, a maternal mortality rate of 6.8 per cent. This compares favorably with the maternal mortality rate throughout the United States. Further analysis of this group will reveal that, regardless of the type of treatment, the maternal mortality rate from toxemia at this institution for the past 15 years has remained relatively constant. Table I lists the causes of death for the 15 patients. It is immediately apparent that 9 out of 15 died of cardiovascular or renal complications. Three of these had special significance and have been reported in detail.⁴ The death rate was three times greater in multigravidae than it was in primigravidae. In general, our experience has been that the patients who die are those in the latter years of re-

productive life who have chronic cardiovascular disease and/or chronic renal disease. The typical young primigravida with eclampsia seldom dies. This thought leads one to interject that a more liberal sterilization policy for patients with cardiovascular and renal diseases would be effective in reducing the maternal mortality rates.

Fetal survival

There were 210 babies delivered in the hospital, and, of these, 38 per cent weighed less than 2,500 grams and 4 per cent weighed less than 1,000 grams. The uncorrected fetal mortality rate was 23.5 per cent.

Treatment

Since the cause of toxemia is not yet fully appreciated, treatment remains an effort to correct the known derangements of physiology. We believe that a rational therapeutic regimen should include the following steps in order: (1) control of convulsions; (2) relief of angiospasm; (3) correction of abnormal fluid distribution; and (4) termination of pregnancy.

The details of our management of eclampsia have been given in previous reports, and it is not necessary to repeat them here.^{2, 3} A number of modifications have evolved during the past 5 years. Perhaps the most significant of these advances has been the addition of the antihypertensive drugs to our armamentarium. With the advent of such drugs as hydralazine and reserpine, the action of which is very predictable, the management of toxemia has been simplified. The ease of administration of these drugs and their effectiveness have diminished the necessity of such procedures as regional anesthesia for the control of blood pressure. We have discarded the use of intramuscular magnesium sulfate in the treatment of toxemia.

Control of convulsions. Even though it might not be considered significant, Table II indicates that the greater the number of convulsions the greater the fetal loss. The same thing can be said for maternal mor-

Table I

<i>Cause of death</i>	<i>No.</i>
Cerebral hemorrhage	4
Circulatory collapse	3
Cardiac failure	2
Pulmonary embolus	1
Ruptured uterus	1
Respiratory obstruction	1
Unknown	3
Total	15

Table II

No. convulsions	Patients	Maternal mortality (%)	Fetal mortality (%)
1	80	6.3	12.2
2-5	100	6.0	20.5
6-10	26	3.8	24.8
10+	13	23.0	27.0

tality only after the number of convulsions has reached ten.

The initial control of convulsions is best done by the intravenous administration of sodium amobarbital in doses varying from $3\frac{3}{4}$ to $7\frac{1}{2}$ grains. This may be repeated subsequently if necessary. An intramuscular injection of phenobarbital in doses varying from 1 to 3 grains is given every 6 hours. If a patient is in labor or experiencing pain from some other cause, meperidine HCl (Demerol) should be included as a part of the sedation. We do not use morphine because of its depressive effects on the fetus and mother.

For the past 5 years we have used reserpine extensively in the management of toxemia of pregnancy. The chief function appears to be the control of angiospasm; however, it should be pointed out that the tranquilizing effects have been most beneficial. We have theorized that toxemia of pregnancy is due to superactivation of the hypothalamus with the resulting effects being produced by this overactivity.⁵ If this be true, the action of reserpine blocking activity at the hypothalamic level is specific for toxemia. The use of reserpine (Serpasil), 2.5 to 5.0 mg. every 4 to 6 hours, either intramuscularly or intravenously, has enabled us to reduce the amount of barbiturates by one half. Prior to the use of Serpasil it was not unusual for a patient with eclampsia to require 15 to 20 grains of amobarbital (Amytal) plus 9 to 12 grains of sodium phenobarbital (Luminal) per 24 hours for sedation. The same condition can now be adequately controlled with one third to one half that amount barbiturate in addition to Serpasil.

Even though it is probably of questionable significance, when one analyzes the time of day of convulsions the impression is obtained that many more eclamptic convulsions occur between the hours of 4 A.M. and 8 A.M. If this is a valid observation, a possible explanation is found in the fact that cerebral edema is aggravated when the patient lies down. This increase in cerebral edema might be the cause of early morning convulsions.

Control of angospasm. The interest in this department has been shifted toward the use of antihypertensive drugs as a means of controlling angospasm because we believe there are now a number of drugs available that are effective and safe. The introduction of continuous caudal and continuous spinal anesthesia in this institution for the control of blood pressure in 1945 and its use during the years 1945 through 1951 was accompanied by a reduction in the maternal mortality rate to less than one third that of the preceding 5 years (Table III).

Table III

	1941-1944	1945-1949	1950-1951	1952-1958
Number patients	100	100	50	220
Sedation only (%)	94	34	34	45
Regional anesthesia (%)	6	66	66	10
Hypotensive drugs (%)	0	0	0	45
Maternal mortality (%)	14.0	4.0	4.0	6.9
Fetal mortality (%)	20.0	23.5	17.0	20.0

Table IV

Method	No. patients	Maternal mortality (%)	Fetal mortality (%)
Regional anesthesia	21	4.7	24.0
Sedation only	85	9.4	24.0
Hypotensive drugs	96	4.2	23.0

In Table IV it will be noted that regional anesthesia and antihypertensive drug therapy had equally good results as far as maternal and fetal mortality was concerned. Even though the maternal and fetal survival rates obtained through the use of regional block have not been improved, the use of antihypertensive drugs has almost completely replaced this means of controlling angiospasm in this department. There are two reasons for this therapeutic change. First, antihypertensive drugs can be administered without special training or equipment, and, second, the use of antihypertensive agents carries less potential hazard to the patient. Sedation alone is unsatisfactory as illustrated by the high maternal mortality among patients treated in this manner. It should be emphasized that regional anesthesia is an acceptable technique and it is still used for the occasional patient who does not respond to drugs or who has severe cardiac decompensation as a complication of toxemia.

Hydralazine (Apresoline), in doses of 10 to 20 mg., is given intravenously or intramuscularly and repeated at intervals of one to 4 hours as needed to produce a desired effect in lowering blood pressure. In addition, Serpasil, 2.5 to 5 mg., is given intravenously or intramuscularly every 4 to 6 hours. If this is insufficient to adequately control the blood pressure, continuous caudal anesthesia is instituted.

Correction of abnormal fluid balance. It has long been recognized that patients with severe degrees of toxemia have an overdistended interstitial fluid compartment with a normal or reduced intravascular compartment. There is often hemoconcentration as evidenced by an increase in the hematocrit. Other evidence of dehydration includes the dry mucous membranes and the fact that the patients are thirsty and will drink large quantities of water if permitted to do so. This occurs in spite of the fact that the sodium concentration in the plasma is most frequently found to be slightly low.⁶ This could mean that water has been retained preferentially, and this in excess of sodium,

or that the sodium has been shifted into some as yet undetected area.

For the past 8 years it has been our policy to use water as the diuretic of choice in severe toxemia of pregnancy. If the patient is rational and able to take fluids by mouth she is encouraged to do so. Many will consume in excess of 4,000 c.c. per 24 hours of their own volition. However, if they are unwilling or unable to drink, the fluids are given intravenously in the form of 5 per cent glucose in distilled water. One thousand cubic centimeters of 5 per cent glucose is given intravenously every 6 hours at a rate of approximately 60 drops per minute.

A diuresis will normally be established after 36 to 48 hours of fluid administration. In almost every patient, at the end of 48 hours, the output will exceed the intake. During the first few hours of fluid administration the edema may become more pronounced but after the diuresis is established the edema will clear rapidly. If a diuresis has not been established within 48 hours, the fluid intake must be reduced. A low serum protein concentration is frequently responsible for a failure to clear edema fluid. If the serum protein level is found to be low, this should be restored by giving whole blood, plasma, or concentrated albumin. In the majority of patients, "hydration therapy" is satisfactory and additional diuretics are not needed. In an occasional patient chlorothiazide, 500 mg. every 12 hours, is given to stimulate the flow of urine. As long as the rate of administration of fluid has not exceeded 1,000 c.c. per 6 hours, cardiovascular overload has not been a problem.

Another addition to our management of the eclamptic patient has been the use of

Table V

Time in hospital prior to delivery (hours)	No. patients	Maternal mortality (%)	Fetal mortality (%)
0-24	109	10.0	19.0
24-48	30	10.0	21.0
48+	56	1.8	27.0

Table VI. Method of delivery

	<i>Vaginal</i>		<i>Cesarean section</i>
	<i>Spontaneous labor</i>	<i>Induced labor</i>	
Maternal mortality (%)	4.3	5.8	5.9
Fetal mortality (%)	19.1	38.0	30.0
Premature (%)	35.5	56.0	70.0
Immature (%)	2.1	5.8	10.0

intravenous alcohol. Alcohol has a theoretical advantage of producing diuresis, sedation, and vasodilatation. We have not been able to demonstrate much effect in this regard. The reason for the continuing use of intravenous alcohol is the number of calories supplied by the alcohol. These patients need some caloric intake and alcohol supplies 7 calories per cubic centimeter of 95 per cent alcohol. We frequently add as much as 75 c.c. of 95 per cent alcohol to each of two intravenous infusions per 24 hours. This gives an intake of approximately 1,000 calories from the alcohol alone.

Termination of pregnancy. It is generally recognized that the most effective treatment for eclampsia is the termination of pregnancy. This, we agree, is exceedingly important and should be accomplished by the most conservative method as early as the patient's condition will permit.

It is important that the above steps to correct the disturbed physiology be taken first so that at the time of the termination

of the pregnancy the patient will be as nearly in physiologic balance as possible. In Table V it will be noted that the lowest maternal mortality rates were in those patients who were delivered after 48 hours of hospitalization. This did not seem to offer any improvement in the fetal mortality rate. It has been our policy to treat the patients approximately 48 hours prior to the consideration of termination of pregnancy. Most patients with eclampsia will have a spontaneous onset of labor prior to 48 hours' hospitalization. The technique of termination of pregnancy seems to have little effect on maternal survival, but the best fetal survival rates were obtained in those patients who were delivered vaginally after spontaneous labor rather than by cesarean section or the induction of labor (Table VI).

After the allotted 48 hours of therapy if labor has not ensued spontaneously a sterile vaginal examination is made to determine the condition of the cervix. If the cervix is ripe and if, in the opinion of the examiner, labor can be induced, this is done with use of intravenous oxytocin drip. The use of the intravenous oxytocin induction technique has reduced the cesarean section rate in eclampsia from 19 per cent as reported by Turner, DeLozier, and Whitacre³ to 8.9 per cent in the present series.

Of those patients who were delivered vaginally, 55 per cent were delivered spontaneously, 40 per cent by episiotomy and low forceps, and 5 per cent by other means, such as midforceps and breech extraction.

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Acute fatty metamorphosis of the liver in pregnancy

Report of a case complicating toxemia in pregnancy

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IN THE past several years there have been few articles in the obstetric literature concerning liver disease in pregnancy. The principal topics have been infectious hepatitis and acute yellow atrophy.

A variant of acute yellow atrophy was described by Sheehan¹³ in 1940. The clinical features of this disease, which Sheehan termed "obstetric acute yellow atrophy," are identical with those of acute yellow atrophy. However, the microscopic appearance of the two diseases are distinctly different, the former presenting fatty metamorphosis and the latter cellular necrosis.

It is the purpose of this report to present a case in which a liver lesion similar to the one described by Sheehan complicated a pregnancy. This is the first report of a case in which there was no associated jaundice.

Clinical course. The patient, M. M. (UHNA-31211), a 42-year-old white woman, was seen April 1, 1958, because of amenorrhea of 4 months' duration and occasional nausea and vomiting. She had had an appendectomy in 1930 and some menstrual irregularity in 1956. Since then menses had occurred every 28 days and lasted 4 days.

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Physical examination disclosed moderate obesity, blood pressure of 140/80, and uterine enlargement to one fingerbreadth below the umbilicus. The patient had been normotensive previously. Routine antenatal studies were within normal limits.

The frequent occurrence during the next few months of hypertension, excess weight gain, and ankle edema necessitated the use of chlorothiazide* and a low-salt diet. On August 5, at approximately 39 weeks' gestation, the patient was hospitalized for 3 days because of persistent headaches, blurring of vision, ankle edema, and blood pressure of 160/100. Treatment with a low-salt diet, phenobarbital, and chlorothiazide resulted in a 6 pound weight loss and a blood pressure that fluctuated between 126/70 and 142/90.

After discharge from the hospital the patient was well until August 15, when an episode of nausea and vomiting occurred. Intermittent nausea and vomiting associated with substernal burning persisted until the patient's second hospital admission on August 23. Physical examination disclosed no abnormalities except slight dryness of the mucous membranes and blood pressure of 150/100. The cervix was 1 cm. dilated and 20 per cent effaced, and the vertex was floating. A urine specimen obtained on admission contained 2 to 4 red blood cells and 3 to 4 white blood cells per high-power field and one-plus albumin.

No nausea or vomiting was noted after admission to the hospital; however, intravenous

*Diuril, a product of Merck Sharp & Dohme.

fluids, pyridoxine, phenobarbital, and prochlorperazine* were administered for 2 days.

Since the blood pressure remained at 140-150/90, Mio-pressin No. 1† was started on the third hospital day. On the fourth hospital day induction of labor with intravenous Pitocin was attempted. Later that same day hydralazine hydrochloride,‡ 20 mg., was administered intramuscularly because of a recorded blood pressure of 176/90. The blood pressure became normal.

The following day Pitocin induction was attempted again. The patient's pulse, which formerly ranged from 94 to 128, remained over 130 during the entire period of Pitocin administration. Because of the persistent tachycardia and hypertension, 5 mg. of reserpine was injected intramuscularly. There was no change in the tachycardia or hypertension, so the reserpine was repeated 7 hours later. Thirty-five minutes after the second dose the reclining blood pressure was recorded at 80/60. Fifteen minutes later the blood pressure, without further treatment, had returned to 108/70. During the night the blood pressure varied between 90/50 and 110/70 and the pulse between 102 and 120. The fetal heart rate remained about 140.

The next morning, the sixth hospital day, the patient received reserpine, 0.1 mg., orally. Her condition remained satisfactory until 3:30 P.M. At that time, while walking to the bathroom, she experienced some dizziness and fell to her knees. While she was in this squatting position, her eyes were fixed on the ceiling and the muscles of the upper extremities and face were jerking spasmodically. The blood pressure was 90/0.

Physical examination revealed no neurological abnormalities or evidence of external injury. There was some drowsiness, but the patient responded readily to questioning. The blood pressure in bed was 116/58. Fetal heart tones were now absent. An electrocardiographic tracing was interpreted as normal.

During the night the patient's blood pressure ranged from 70/50 to 118/72 and the pulse

from 72 to 100. On two occasions she vomited a small quantity of blackish material.

The following morning, the seventh hospital day, the patient vomited several times. A generalized convulsion followed one of the episodes of vomiting, and all cardiorespiratory activity ceased. Artificial respiration was instituted immediately, and 1 c.c. of epinephrine was injected into the heart. Cardiorespiratory activity returned in a few minutes, but the patient remained comatose. Other major physical findings included an absent corneal reflex, a positive Babinski reaction on the right, and bilateral moist râles.

An assisted respirator (Bennett valve apparatus) and intravenous vasopressors were used to maintain the vital functions.

An hour after the cardiac arrest, meconium-stained fluid was noted to be leaking from the patient's vagina. Upon pelvic examination the cervix was found to be 6 cm. dilated. The vertex was presenting at plus-one station. No uterine contractions were evident. In the hope that emptying the uterus would enhance respiratory activity, an attempt was made to deliver the baby. This was unsuccessful, and, 9 hours later, after progressive deterioration, the patient died undelivered.

Necropsy findings.

Gross. There was no evidence of jaundice in the sclera or skin. Hemorrhagic phenomena were observed in the following: anterior mediastinum, and area 7 by 7 by 0.5 cm.; left pleural cavity, 800 c.c. blood (800 c.c. clear fluid in the right pleural cavity); subendocardial surface of the upper interventricular septum, and the anterior papillary muscles of the left ventricle. The bases of both lungs, on section, presented dark red wet spongy surfaces. The trachea and bronchi contained a small amount of material resembling the gastric contents. There was a jet black discoloration of the mucosa of the esophagus which extended from the hypopharynx to the cardiac sphincter.

The liver was of normal size, weighing 1,400 grams, and was smooth, pale yellow, and soft. The cut surface was pale yellow and without distortion.

The kidneys were pale tan and on the cut surface demonstrated deep V-shaped scars.

The brain was normal except for some softening of the pituitary gland.

The cervix was fully dilated and not lacerated. A male fetus weighing 3,070 grams lay

*Compazine, a product of Smith Kline & French Laboratories.

†Smith Kline & French Laboratories (12.5 mg. rauwolfia serpentina, 0.1 mg. protoveratrine, 2.5 mg. dibenzyline).

‡Apresoline, a product of Ciba Pharmaceutical Products, Inc.

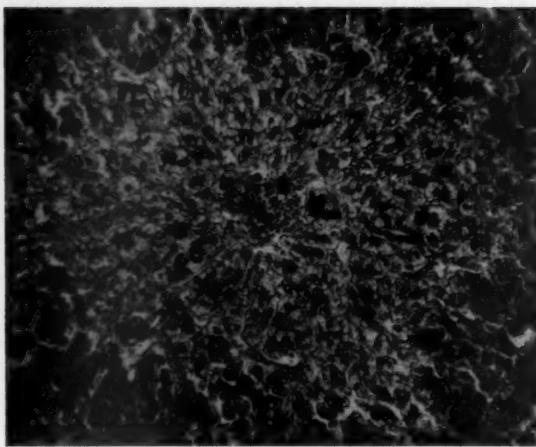


Fig. 1. Liver. Pale area of fatty metamorphosis in the central half of the lobule surrounded by a darker rim of normal liver cells. (Hematoxylin and eosin. $\times 50$; reduced $\frac{1}{2}$.)

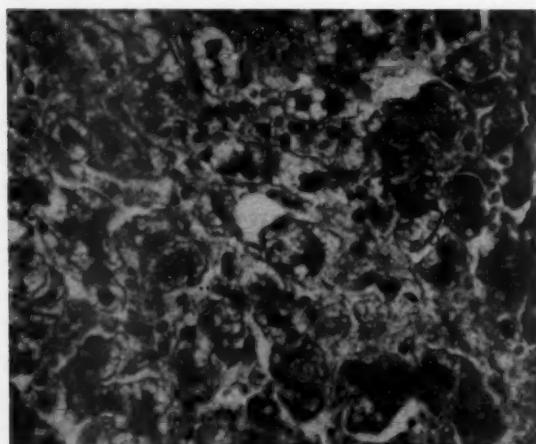


Fig. 2. Liver. Distended liver cells with innumerable tiny vacuoles and central nuclei. (Hematoxylin and eosin. $\times 230$; reduced approximately $\frac{1}{2}$.)

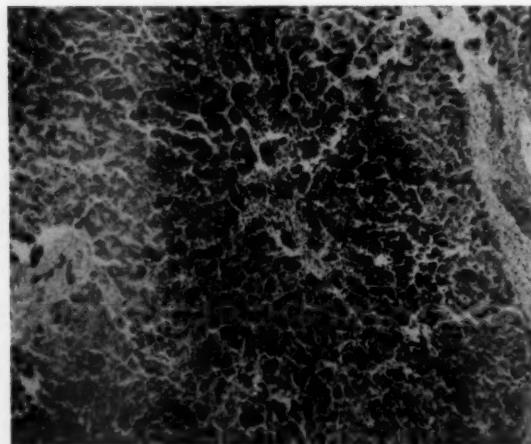


Fig. 3. Liver. Positive stain for fat in central lobular cells. (Oil Red O. $\times 50$; reduced $\frac{1}{2}$.)

in the uterus in a cephalic presentation. Except for some maceration of the scalp all the organs of the fetus were normal in size, weight, and relationships. The placenta was normal.

Microscopic. Lesions of note were present in the liver, kidneys, esophagus, lungs, pituitary, and heart.

LIVER. Hepatic lobular architecture was preserved with normal portal triads. Central lobular fatty metamorphosis without inflammatory cell infiltration or necrosis was present in the central 30 to 50 per cent of all lobules (Fig. 1). The affected cells had sharp cytoplasmic borders and contained multiple small cytoplasmic vacuoles. The nuclei were normal and central in position. Sinusoids were slightly dilated, and bile stasis was absent (Fig. 2). On staining with Oil Red O, neutral fat was evident in the vacuoles of the central lobular parenchymal cells (Fig. 3).

KIDNEY. On staining with hematoxylin and eosin the kidneys were normal. However, on Oil Red O staining, neutral fat in moderate amounts was discovered in the tubules of the medullary rays.

ESOPHAGUS. Heavy infiltrations of neutrophils and chronic inflammatory cells were present in all layers of the esophagus. Extensive esophageal mucosal ulceration was present.

LUNGS. In lung sections bronchopneumonia was evident.

PITUITARY. In the pituitary, normal architecture was interrupted by scattered areas of acute infarct necrosis affecting both the anterior and posterior lobes.

HEART. Apart from the subendocardial acute hemorrhages, also noted grossly, the heart was normal.

OVARIES. The ovaries were normal.

Anatomical diagnosis. Diagnosis was fatty metamorphosis of the liver; acute panesophagitis; subendocardial and anterior mediastinal hemorrhages; acute focal necrosis of the anterior and posterior portions of the pituitary; bronchopneumonia.

Comment

The accumulation of fat in the parenchymal cells of the liver has been attributed variously to nutritional deficiency, hormonal disturbance as in diabetes, oxygen lack, and toxic or infectious agents.

Microscopically, this fatty change in the liver is varied in distribution. The globules

of fat in the parenchymal cells are large and tend to push the nuclei into eccentric position. There may or may not be necrosis and leukocytic infiltration.

In contrast, the fatty change in the liver in obstetric acute yellow atrophy characteristically affects the central two thirds of each lobule. There is some variation in extent in the different lobules, but there always is a periportal rim of apparently normal liver cells. The affected parenchymal cells are bloated and filled with innumerable tiny vacuoles of fat. The nuclei of these cells are normal and central in location. Lobular architecture is normal, and there is no evidence of recent or healed necrosis. There is no significant cellular infiltration.

The extent of lobular involvement in this case is less than usually described. This probably explains the absence of jaundice. Perhaps if the patient had lived longer, the liver would have been more severely involved and jaundice would have appeared.

In addition to the changes in the liver, several of the reported cases and this case showed fatty infiltration of the renal tubules. The significance of this finding is unknown.

Most authors agree that the fatty metamorphosis of the liver in pregnancy described by Sheehan¹³ is a distinct histologic entity. However, similar changes in the liver are observed in chronic hyperemia of the liver, early carbon tetrachloride intoxication, and nutritional disturbance in animals.^{4, 11} In acute fatty metamorphosis of the liver in pregnancy, experimental and clinical evidence would seem to favor nutritional disturbance.¹¹ This could apply readily in the present case. Lynch and associates⁸ described a case of obstetric acute yellow atrophy in which there was associated hyperthecosis. They believed that the liver changes possibly could be secondary to an unduly high or abnormal output of ovarian hormones. No hyperthecosis was evident in our case. Oxygen lack has been mentioned as a factor responsible for a fatty change in the liver. Certainly, in this patient, a moderate amount of anoxia secondary to the hypotension was present. However, it is

doubtful whether the anoxia was of sufficient severity or duration to be a chief contributing factor. When considering the possible etiological influence of drugs in this case, only the drugs administered in the hospital need be included. The duration of hospitalization makes it unlikely that any agent taken prior to admission influenced the liver disease. Of the drugs administered during hospitalization, only phenobarbital⁵ and prochlorperazine⁹ have caused liver disease, but the histologic appearance in such instances is distinctly different. Reserpine never has been incriminated as a cause of liver disease, and we do not believe it produced the liver lesion in our patient.

The other interesting aspects of this case are the persistent hypotension and the cardiac arrest.

The severe hypotension which occurred was attributed primarily to the effect of drugs. Several hypotensive agents were used, and their action may have been prolonged by the damaged liver; however, the time sequence of events would seem to incriminate reserpine alone. Reserpine has been established in numerous studies as a mild and safe hypotensive agent.^{1, 2, 3, 6, 10} However, on occasion, excessive hypotension following its parenteral administration has been observed.^{1, 3, 12} The liver, along with other organs, is involved in the inactivation of reserpine.^{7, 14} The damaged liver in this case could have contributed to the exaggerated drug response. However, a normal response to reserpine is the usual pattern in patients with liver disease, and excessive hypotension following its parenteral use has occurred in patients with normal liver function.

Most of the events that happened prior to this patient's death can be explained. The cardiac arrest, however, occurred at a time when the effect of reserpine had diminished considerably and the patient's general condition was improving. Because of this, it was deemed unlikely that reserpine caused the cardiac arrest. Cerebral anoxemia or a vagotonic reflex associated with the nausea and vomiting would seem

to be the only possible etiological factors. The resultant cerebral damage and the aspiration pneumonitis were responsible for the progressive deterioration and death of the patient.

Summary

A severe hypotensive response to parenterally administered reserpine occurred in a patient with mild toxemia of pregnancy. Later, when the effect of the reserpine had diminished considerably, cardiac arrest developed. Some hours after resuscitation, the

patient died and was found at necropsy to have fatty metamorphosis of the liver.

Acute fatty metamorphosis of the liver in pregnancy is an uncommon lesion. The principal histologic finding was a foamy vacuolar type of fatty change involving the central portion of the liver lobules.

Liver disease was unsuspected in this patient because of the absence of jaundice. The possibility of liver disease should be entertained whenever persistent nausea and vomiting develop in the latter part of pregnancy, especially when severe toxemia and pyelonephritis can be excluded.

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Studies on abruptio placentae

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ABRUPTIO placentae is a unique disease in obstetrics bearing several appellations, such as accidental hemorrhage, premature separation of the normally implanted placenta, and ablatio placentae. The reported incidence of abruptio placentae ranges between one in 85 deliveries and one in 250, depending upon the diagnostic criteria used. For the past few years, special importance has been attached by obstetricians to the disease as the latter has proved to be one of the main causes of afibrinogenemia. It is one of the most important obstetrical complications in view of its special relationship to toxemia and the high mortality rate of mother and child, particularly of the latter, caused by this disease. The present studies have been attempted in order to elucidate special aspects of this disease as related to the present status of public health in Taiwan.

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Material

A statistical review of this disease was made among the deliveries in the Provincial Taipei Hospital covering the period between May, 1956, and June, 1958. Because of the lack of laboratory facilities, a systematic research on coagulation defects was started only from October, 1958, and is still underway. This study was made in Taipei City with a population of 800,000. There are 6 government, 2 missionary, and 1 charity hospitals equipped with modern medical facilities. Over 100 obstetricians and 189 midwives are practicing in this city. Besides these, 11 health stations are in charge of expectant mothers of the indigent class.

Statistical review

Incidence. We found 32 cases of abruptio placentae among 1,532 deliveries during this period. The incidence, therefore, is 2.09 per cent, or one in 48 deliveries. Compared with the incidence reported, our figure seems to be unusually high. This is probably because of the specificity of our hospital for accommodation of abnormal deliveries and because of the fact that the great majority of normal deliveries are home deliveries in Taiwan. Deliveries in Taipei City covering this period were 57,570 and the incidence

Table I. Frequency of abruptio placentae

<i>Author</i>	<i>Frequency (%)</i>
Frankel ¹	0.096
Pankow ¹	0.41
Bland and Rakoff ²	0.93
Hester ³	1.3
Daro ⁴	0.42
Present authors	2.09 (for hospital) 0.16 (for community)

Table II. Age distribution

<i>Age</i>	<i>No.</i>	<i>%</i>
20-29	4	12.5
30-34	10	31.25
35-39	10	31.25
40-49	8	25.0

Table III. Relationship between abruptio placentae and parity

	<i>No.</i>	<i>%</i>
0-1	2	6.25
2-4	5	15.62
5-12	25	75.13
(15)		

Table IV. Reported maternal mortality rate in abruptio placentae

<i>Author</i>	<i>Mortality rate (%)</i>
Ando ⁵	6.0
Hasegawa ¹	20-30
Nakajima ⁶	30
Bland and Rakoff ²	6.3
Crichton ²	10.9
Hester ³	4.0
Present authors	15.62

Table V. Reported fetal mortality rates

<i>Author</i>	<i>Mortality rate (%)</i>
Ando ⁵	70-80
Hasegawa ¹	60-80
Nakajima ⁶	over 70
Greenhill ²	66.4
Hester ³	68
Waddington ⁷	29.84
Present authors	87

of abruptio placentae was estimated to be 92. Therefore, the correct vital statistical incidence should be 0.16 per cent (Table I).

In the last 3 months, since the initiation of the studies on coagulation defects, we found 8 cases of abruptio placentae among 200 deliveries, namely one abruptio placentae in 25 deliveries (4 per cent). This very high figure is apparently attributable to hospital selectivity and seasonal variation.

Table II indicates the relative rarity of this disease below the age of 30.

The high incidence of abruptio placentae in the grand multipara is worthy of note (Table III). The grand multiparous group shows ten times as high an incidence as the primiparous group. The predisposition of the grand multipara to this disease may be accounted for by the chronic vascular changes in the uterus. Abruptio placentae may also be a special manifestation of toxemia superimposed upon the chronic hypertensive vascular change.

Maternal mortality rate. In our series there were 5 deaths, giving a mortality rate of 15.6 per cent. The comparison between the data reported in the literature is given in Table IV.

Three out of 5 deaths resulted from uremia due to acute renal failure after cesarean hysterectomy. In these cases anuria was noted prior to operation. Although no autopsy was performed, anuria and acute sharp rise of nonprotein nitrogen were suggestive of acute bilateral cortical necrosis of the kidney. The other 2 patients died from profound hemorrhage following a vaginal delivery.

Fetal mortality rate. There were 27 fetal deaths among 32 cases of abruptio placentae, giving a fetal mortality rate of 87 per cent (Table V). The high mortality rate is ascribed to the loss of fetal heart sounds at the time of hospitalization and, therefore, to the severity of the separation of the placenta.

In Taipei City hot weather lasts from April to September and cool weather from October to March. The incidence in the

Table VI. Seasonal variations

Month	No. of cases
January	6
February	0
March	4
April	3
May	3
June	0
July	1
August	4
September	3
October	2
November	4
December	2

Table VII. Duration of pregnancy at time of abrupton

Authors	Length of pregnancy (months)				
	6	7	8	9	10
Present authors		5	3	24	
Obata ⁸	6	16	55	74	86

hot season was 14 and that in the cool season was 16. There is, therefore, no difference in incidence between the cool and hot seasons (Table VI).

According to Obata,⁸ abruptio placentae was found not only in the last trimester but also in relatively early pregnancy and no proportional increase of incidence with the advance of pregnancy was observed. The earlier abruptio placentae occurs in pregnancy, the more it resembles an abortion. Thus, between the twentieth and twenty-eighth weeks the picture is very similar to that of an abortion (Table VII).

It is clearly shown by Table VIII that abruptio placentae is inclined to occur in elderly grand multiparas, whereas ordinary

toxemia occurs in the younger group with relatively small parity, particularly in the primipara.

Etiology

It has long been believed that some relationship exists between toxemia of pregnancy and abruptio placentae. Some clinicians even believe that abruptio placentae is a form of toxemia loosely akin to eclampsia. Hertig^{2, 28} claimed that toxic separation of the placenta is a form of "uterine eclampsia" since fatal cases show hepatic lesions which are not distinguishable from those of ordinary eclampsia. From Eastman's clinic Delfs⁹ reported that 47 per cent of patients with the disease gave evidence of hypertension prior to the placental separation. At the Chicago Lying-in Hospital, Dieckmann¹⁰ found that 69 per cent of his patients with abruptio placentae had toxemia. In our series only 3 patients showed no toxemic signs, suggestive of nontoxemic origin. The remainder, namely, 29 cases (90.6 per cent), revealed proteinuria, hypertension, or elevated NPN, suggestive of the presence of toxemia or chronic hypertensive vascular disease.

Treatment

Eastman⁹ believed that cesarean section is the procedure of choice in the treatment of patients with uteroplacental apoplexy in the presence of a tetanically contracted uterus showing no sign of relaxation with the cervix not dilated to an appreciable extent. On the other hand, conservative methods are indicated in partial separation with slight or controllable bleeding. In Eastman's⁹ clinic the incidence of cesarean section is 37.7 per cent and in Pennsylvania

Table VIII. Incidence of toxemia

	Age			Parity			Total
	20-29	30-39	40-49	0-4	5-9	10-15	
Pre-eclampsia, mild	58	45	4	95	21	1	107
Pre-eclampsia, severe	33	23	1	44	12	1	57
Eclampsia	23	3	3	25	3	1	29
Abruptio placentae	4	20	8	7	20	5	32

Table IX. Blood coagulation and coagulation factors in cases of abruptio placentae

<i>Case No.</i>	<i>Initials</i>	<i>Bleeding time</i>		<i>Coagulation time</i>	<i>Prothrombin time</i>	
1	S. H. Y.	14 minutes, 30 seconds		No coagulation	No fibrin	
2	H. H. K.	2		30 minutes	30 minutes, 4 seconds	
3	C. R. Y.	7		No coagulation	3	
4	H. K. P. S.	3	20	4 minutes, 10 seconds	19	5
5	H. Y. C.	7	30	5	16	2
6	H. Y.	5	30	85	43	30
7	H. S. M.	5	30	5	43	13
8	Y. W. P. Y.	12	30	20		

Hospital²⁸ 81.0 per cent. With the advent of the concept of afibrinogenemia and availability of fibrinogen preparations, the modern trend of treatment of abruptio placentae is steadily being changed to more conservative procedures, namely, artificial rupture of membranes, use of Pitocin, and administration of blood transfusion and fibrinogen. In the series of Daro,⁴ cesarean section was performed in 12.1 per cent of 37 patients. The incidence of cesarean section in our series is 65.6 per cent. This is partly due to the severity of the disease in patients referred to our hospital, as evidenced by the necessity of cesarean section to control bleeding on account of lack of fibrinogen preparations and to the financial inability of some of the patients to obtain sufficient blood transfusions.

Coagulation defects

An occasional detection of afibrinogenemia in abruptio placentae even by infrequent examination of coagulation defects has inspired us to make a systematic study on this subject since October, 1958, and, in the course of 2 months from October to December, 1958, we observed coagulation defects in 8 cases of abruptio placentae.

The methods adopted for these studies

were as follows: bleeding time: Duke method¹¹; clotting time: Lee-White method¹²; platelet count: Fornio method¹³; clot retraction: MacFarlane method¹⁴; prothrombin time: one-stage prothrombin time of Quick¹⁵; fibrinogen: Andersch and Gibson's¹⁶ modification of the method of Wu and Ling after preparation of fibrinogen following Seegers^{18, 20}; fibrinolysin: method of Astrup and Muellerts^{17, 18} for the determination of fibrinolytic activity; fibrinogenolysin: addition of 0.03 ml. of plasma to 5.0 ml. of saline and 5.0 ml. of 1 per cent fibrinogen* solution; this mixture is incubated for 24 to 48 hours at 37° C. and the reaction is then stopped and the amount of clottable fibrinogen determined by the above-mentioned method; Ac-globulin: two-stage method of Warner, Brinkhous, and Smith modified by Johnson and Seegers.¹⁸

According to Lewis,²¹ failure of the clotting mechanism of the blood may occur in up to 5 per cent of cases of severe concealed hemorrhage, while Reid^{22, 23} reported that only 10 per cent of patients with abruptio placentae had severe coagulation defects and one third of the patients had hypofibrinogenemia. As Table IX shows, to our

*Fibrinogen is prepared as a 1 per cent solution containing 10 per cent imidazole buffer in volume (pH 7.25).

Platelet count	Retraction (%)	Fibrinogen level (mg./dl.)	Prothrombin (units)			Fibrinogenolysin	Fibrinolysin
			+ Saline	+ Ac-globulin	Differential		
106,200	-	0	20.3 (19.5%)	104.0 (100%)	83.7 (80.5%)	plus × 100	plus × 100
89,280	-	0	20.0 (17.9%)	111.3 (100%)	91.3 (82.1%)	-	-
26,050	64	0	0.0 (0%)	20.6 (100%)	20.6 (100%)	-	-
108,280	68	150	33.4 (53.4%)	62.5 (100%)	29.1 (46.6%)	-	-
64,400	60	260	50.0 (39.2%)	127.5 (100%)	77.5 (60.8%)	-	-
51,250	-	0	15.3 (24.5%)	62.5 (100%)	47.2 (75.5%)	-	plus 1/100
48,790	43	215	145.0 (77.3%)	187.5 (100%)	42.5 (22.7%)	-	-
27,170	-	0	23.8 (45.8%)	51.9 (100%)	28.1 (54.2%)	-	-

surprise only 3 patients showed normal fibrinogen levels while 5 exhibited afibrinogenemia. From Table IX, it is also apparent that prolonged prothrombin times and thrombocytopenia are frequent concomitant findings, whereas fibrinolysin was demonstrated in only 2 cases and it then disappeared after blood transfusions, and the presence of fibrinogenolysin was suspected in only one other case (contrary to Phillips, Montgomery, and Taylor's findings²⁴). It is noteworthy that a large differential is found on measurement of Ac-globulin activity by the two-stage method, suggesting a deficiency of this factor.

Effect of blood transfusion on afibrinogenemia

According to Reid,^{22, 23} in order to correct the clotting defects and combat shock, the predelivery requirement in the average patient is 1,500 to 2,000 ml. of blood and 4 to 8 Gm. of fibrinogen. Weiner and associates²¹ recommended that 2 to 4 Gm. of fibrinogen should be given repeatedly until the clotting mechanism is normal; usually no more than 10 Gm. is likely to be needed. They stated that blood transfusion must be given to revive the patient, but the giving of blood in itself is not enough,

one pint increasing the blood fibrinogen concentration by only 5 to 10 mg. per 100 ml. It seems that the consensus of the most outstanding obstetricians is that blood transfusion should be supplemented by fibrinogen in order to restore the normal fibrinogen level. In Taiwan, nonavailability of fibrinogen preparations forced us to use fresh blood to combat this condition, and, as Table X shows, fresh blood transfusions of 1,000 to 2,000 ml., without any supplement of fibrinogen, elevated the fibrinogen above the critical level and controlled bleeding in a matter of hours. In contrast to this, stored blood without supplementary fibrinogen failed to cure this condition (Table XI).

In an attempt to find an explanation for the divergence between the effects of transfusions of fresh and stored blood, we made a brief observation of the effects of storage of blood on its contents. The results are summarized in Table XII.

Contrary to other reports^{25, 26} no remarkable loss of platelets was observed in our study. In contrast to the findings of Taylor and associates,^{25, 27} there was an occasional marked decrease in fibrinogen. As described in the literature,^{25, 26} the prothrombin time was prolonged. Deficiency of Ac-globulin was frequently suggested. It would seem

Table X. Effect of fresh blood transfusion on coagulation defects

Name	Amount of blood transfusion (c.c.)	Hours after blood transfusion	Bleeding time	Coagulation time	Prothrombin time	Fibrinogen (mg./dl.)
S. H. Y.	2,000	14	minutes, 30 seconds	No coagulation	No fibrin	0
		½	12	9 minutes	16.6 seconds	160
		18	3	4 minutes, 30 seconds	11.3	250
		42	4	6 50	10.8	310
H. H. K.	1,300	More than 2 hours		More than 30 minutes	30.4	0
		13	11 minutes	7 minutes, 30 seconds	14.4	200
		20	4	6 20	14	230
Y. W. P. Y.	1,000	12 minutes, 30 seconds		20	No fibrin	0
		½	11	8	40	18 seconds
		5	13	8	30	17.7
						190

Table XI. Effect of stored blood transfusion on coagulation defects

Name	Amount of blood transfusion (c.c.)	Hours after blood transfusion	Bleeding time (minutes)	Coagulation time	Prothrombin time	Fibrinogen (mg./dl.)
C. N. Y.*	750	4	49	Incomplete, 30 minutes	No fibrin	0
	500		20	20 minutes, 30 seconds	23 seconds, small	0
	10		15	Incomplete, 20 minutes	20.6	0

*7:50 P.M. January 14, artificial rupture of membrane and blood transfusion; 2:45 A.M. January 15, craniotomy; 8:15 A.M. January 15, died.

Table XII. Effects of storage of blood on its contents

Days from the extraction of blood to determination	Platelet count	Prothrombin time	Fibrinogen (mg./dl.)	Prothrombin (units)		
				+ Saline	+ Ac-globulin	Differential
6	200,900	15.7 seconds	220	4.6 (7.2%)	63.8 (100%)	59.2 (92.8%)
7	174,800	16.0	180	46.9 (17.0%)	275.6 (100%)	228.7 (83.0%)
7	145,700	13.4	140	47.5 (33.8%)	140.0 (100%)	92.5 (66.2%)
8	214,200	16.6	245	133.8 (81.7%)	163.8 (100%)	30.0 (18.3%)
8	160,710	18.5	200	27.8 (19.5%)	142.5 (100%)	114.7 (80.5%)
8	187,200	13.9	250	41.9 (32.5%)	128.8 (100%)	86.9 (67.5%)
9	172,800	18.5	240	33.4 (41.8%)	80.0 (100%)	46.6 (58.2%)
9	184,300	27.0	230	12.0 (24.1%)	49.8 (100%)	36.8 (75.9%)
9	220,800	23.4	167	20.3 (39.0%)	52.0 (100%)	29.7 (61.0%)
10	172,050	18.5	200	27.8 (19.5%)	142.5 (100%)	114.7 (80.5%)

likely that the excellent effect of fresh blood on coagulation defects in our series was due to its integrity of platelet, prothrombin, fibrinogen, and Ac-globulin, although some unknown factor in fresh blood might have stimulated the endogenous production of fibrinogen.

Paper electrophoresis of serum protein in abruptio placentae

As Table XIII shows, the change in electrophoretic pattern of serum proteins in abruptio placentae consists of a decrease in plasma protein, albumin, and A/G ratio and an increase in α_1 -, α_2 -, and β -globulin. The extent of deviation from the normal female pattern (Table XIV) lies between normal pregnancy, hydatidiform mole, and eclampsia. It is noteworthy that in cases of afibrinogenemia electrophoresis of plasma runs as does that of serum, offering a new diagnostic tool for this particular condition (Fig. 1). This finding is due to the lack of fibrinogen in plasma of the patients.

Comment

Based on the statistical data, it is recommended that elderly grand multiparas with hypertensive vascular disease or toxemia should be placed under special prenatal supervision. A high incidence of afibrinogenemia was noted in a small series of cases of abruptio placentae during a short period in our clinic. Whether it was due to a sampling error or not awaits further investigation. It is noteworthy that in 3 cases there was a large differential of Ac-globulin activity suggestive of deficiency of Ac-globulin. Because transfusion of a large amount of stored blood without supplement of fibrinogen failed to raise the fibrinogen level and to correct the coagulation defects, while fresh blood, also without any supplement of fibrinogen, could do so in a matter of hours, it is evident that the fresh blood is equivalent to the stored blood with supplement of fibrinogen in restoring the coagulation defects of afibrinogenemia. From the therapeutic point of view, too, the transfusion of fresh blood seems to be more rational than

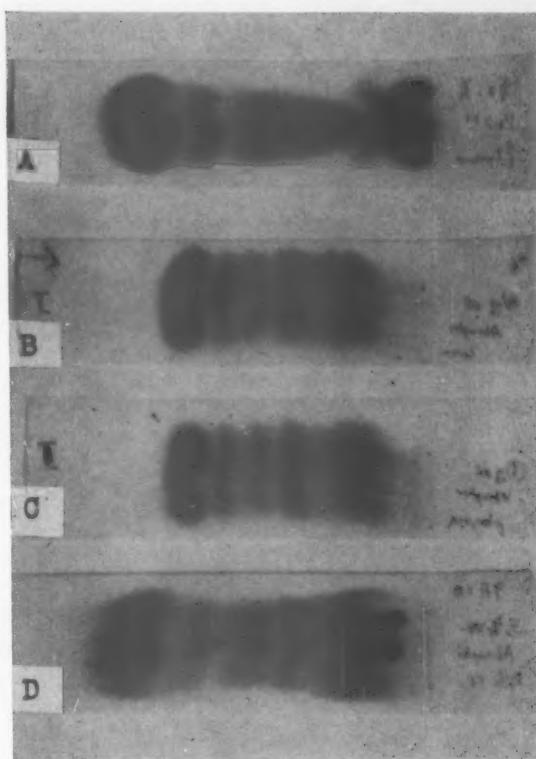


Fig. 1. Electrophoretic patterns in patients with abruptio placentae. A, Plasma of normal pregnant woman; B, serum of patient with abruptio placentae; C, plasma of patient with abruptio placentae; D, plasma of the same patient after operation.

the use of stored blood, for the latter necessitates the additional use of fibrinogen, which may cause homologous serum jaundice.

In our experience, the occurrence of afibrinogenemia is not always synchronous with the onset of severe bleeding in abruptio placentae. Often the afibrinogenemia developed a considerable number of hours before any severe vaginal or intra-abdominal bleeding and before delivery of the fetus. The bleeding was often controlled to such an extent as to allow cesarean hysterectomy in spite of incomplete restoration of the fibrinogen level, which, however, further improved after the operation. Perhaps this further improvement resulted from removal of the placenta as a source of fibrinogen deprivation. Therefore, it would seem to be advisable to set an appropriate time for the delivery,

Table XIII. Serum protein of abruptio placentae (with use of paper electrophoresis).

Case No.	Initials	Plasma protein	Albumin	α_1	α_2	β	γ	Total-G	A/G
1	C. C. G.	7.03	44.6	7.6	8.69	16.38	21.73	56.4	0.805
2	K. C. P.	7.03	48.9	7.77	7.77	12.2	23.31	51.1	0.94
3	L. K. S.	6.29	35.2	7.2	8.0	18.4	31.2	64.8	0.545
4	H. H. S.	5.92	34.9	12.11	13.62	16.7	22.7	65.1	0.535
5	F. P. C.	7.03	41.2	4.86	9.7	17.54	26.7	58.8	0.702
6	R. P. Y.	5.55	45.5	6.61	7.33	18.15	22.3	54.8	0.834
7	H. H. K.	5.55	37.2	5.9	9.2	16.9	29.6	62.8	0.59
8	H. Y.	4.07	38.8	9.5	10.1	15.4	26.2	61.2	0.63
9	H. Y. C.	5.55	44.3	5.8	6.4	13.5	30.0	55.7	0.8
10	S. H. Y.	5.92	43.3	7.08	8.8	16.8	23.8	46.7	0.76
11	H. S. M.	5.55	33.1	11.9	10.56	19.7	24.6	66.9	0.49
12	Y. W. P. Y.	6.29	38.7	11.4	9.5	14.3	25.6	61.3	0.63
13	H. K. P. S.	5.92	38.3	5.47	10.9	19.1	26.02	61.7	0.62
Average		5.98	40.3	7.94	9.27	16.54	25.68	59.7	0.683

Table XIV. Comparison of serum protein of normal nonpregnant women and women with normal pregnancy, hydatidiform mole, eclampsia, pre-eclampsia, and abruptio placentae

	Plasma protein	Albumin	α_1	α_2	β	γ	Total-G	A/G
Normal nonpregnancy	7.99	52.77	5.01	7.61	10.39	24.75	47.93	1.08
Pregnancy, first trimester	7.89	50.88	5.68	8.69	11.60	22.69	49.11	1.06
Pregnancy, third trimester	7.01	42.73	6.95	10.42	15.75	23.09	57.6	0.75
Hydatidiform mole	6.96	44.37	6.61	9.76	12.28	27.2	55.62	0.66
Eclampsia	6.29	31.64	8.72	14.62	15.57	27.38	68.36	0.52
Abruptio placentae	5.98	40.3	7.94	9.27	16.54	25.68	59.7	0.683
Pre-eclampsia	5.88	35.08	8.78	13.56	17.95	23.8	64.0	0.57

whether by the abdominal or vaginal route and to terminate the labor as rapidly as possible, because of the possibility that the coagulation defect will recur if the labor is prolonged.

Whether or not the rarity of appearance of fibrinolysin or fibrinogenolysis in the systemic circulation is of racial specificity and whether or not it accounts for the satisfactory effect of the fresh blood transfusion without supplementary fibrinogen in this series, merit further investigation.

Summary

1. The incidence of abruptio placentae at Provincial Taipei Hospital is 2.09 per cent of the total deliveries and that in Taipei City is 0.16 per cent.
2. In our small series a high incidence of

afibrinogenemia was seen (62.5 per cent).

3. Elderly grand multiparas with toxemia or chronic hypertensive vascular disease are predisposed to abruptio placentae and should be placed under special prenatal supervision.

4. Coagulation defects in our series were characterized by thrombocytopenia, deficiency of Ac-globulin, prolonged prothrombin time, prolonged bleeding and coagulation times, hypo-, or afibrinogenemia, and the rarity of appearance of fibrinolysin and fibrinogenolysis.

5. Transfusions of fresh blood effected a rise in the fibrinogen level, without the use of supplementary fibrinogen.

6. It is important to terminate the labor as quickly as possible when the fibrinogen level is elevated above the critical level.

7. Paper electrophoresis of the plasma in cases of suspected afibrinogenemia is a rapid and simple tool for the diagnosis of this condition.

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Axial torsion of the pregnant uterus

Report of 3 new cases

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A XIAL torsion of the pregnant uterus is normal if it does not exceed 30 degrees. If the degree of torsion exceeds this figure there may be severe symptoms, especially if the rotation approaches or exceeds 180 degrees. Shock, gangrene, and subsequent peritonitis will occur in patients with severe and uncorrected torsion.

Torsion of the pregnant uterus was first described in cattle by Columbi¹ in 1662 and in the human by Labb  ³ in 1876. Torsion in nonpregnant uteri in humans was noted at autopsy by Times⁶ in 1861 and by Virchow⁷ in 1863. In both of these cases, the patients had uterine fibroids.

Nesbitt and Corner⁴ have collected from the international literature 106 examples of torsion in the pregnant uterus to which they added one case and referred to another. They indicated that age and parity have no etiological influence on this condition. The most common factors influencing the position of the uterus are leiomyomas, pendulous abdomen, diastasis recti, asthenia, transverse lie, ovarian cyst, postoperative adhesions, fetal mechanical movements, and congenital anomalies. Sixty-five per cent of the patients in their series had a clockwise rotation.

The patient with torsion of the uterus usually has acute abdominal pain, often severe, and clinical evidence of shock. Twisting of the corpus on the lower segment and cervix compromises the blood supply and traumatizes the pelvic nerves. Pain, nausea, vomiting, and abdominal tenderness are present. Urgency, dysuria, and/or anuria

may be present. It may be difficult or impossible to pass a catheter through the urethra. On physical examination it may be possible to palpate the tense round ligament stretching diagonally across the abdomen. Vaginal examination may reveal a cervix which permits entry of the examining finger but through which the presenting part is not felt. The usual diagnosis is placental separation, twisted and degenerating pelvic neoplasms, or rupture of the uterus. Early in pregnancy the condition may mimic ectopic pregnancy, acute appendicitis, perforated bowel, or pelvic inflammatory disease.

Complications are abruptio placentae, rupture of the uterus, embolism, pulmonary infarct, abnormal position or presentation, obstructed labor, shock, or death.

Therapy is directed to reducing the torsion by external manipulation when possible and by surgical intervention when the diagnosis is in doubt. Because of the difficulty in diagnosis laparotomy is often resorted to and manual replacement at this time is usually possible. Coexisting lesions or necrosis may require further surgical treatment.

Case 1. (Hospital No. 52539.) The patient was a 27-year-old gravida iii, para ii, with painless vaginal bleeding, in whom roentgenograms confirmed the presence of placenta previa and transverse lie of the fetus. She was only 28 weeks pregnant and conservative management was used until the thirty-fifth week. At that time, in the morning after micturition, she returned to bed and, while turning in an effort to become comfortable, she had sudden and acute abdominal pain, became nauseated, felt faint, and developed shock. On admission to the hospital she had a tense, tender abdomen with

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the fetus still in the transverse position. At laparotomy the uterus was rotated 180 degrees in a clockwise fashion. The posterior surface of the uterus was under the abdominal incision and was covered with tortuous varicosities from 0.5 cm. to 1.5 cm. in diameter. The uterus was easily replaced, and a low, transverse cesarean section was performed with delivery of a healthy female infant weighing 5 pounds, 3½ ounces. The placenta completely covered the cervix and extended both anteriorly and posteriorly. It was also partially separated. Bleeding was brisk and the patient received 2,000 c.c. of whole blood. An uneventful recovery followed.

A subsequent repeat cesarean section has been performed on this patient at term without repetition of the torsion or the placenta previa.

Case 2. (Hospital No. 54434.) The patient, gravida iii, para ii, was 42 years of age. On admission to the hospital it was noted that the fetus was in a transverse position. Following a nonprogressive labor a cesarean section was performed. The uterus was found to be rotated 90 degrees in a clockwise fashion. A large intramural leiomyoma was located in the right portion of the fundus. Numerous varicosities of the broad ligament and uterus made the approach for cesarean section difficult. A classical section was performed. The patient bled freely and 1,000 c.c. of whole blood was given at the time of operation. Both mother and baby did well postoperatively.

Case 3. (Hospital No. 75591.) This patient was also a gravida iii, para ii. She was 37 years of age and was 5 feet, 3½ inches tall. Her usual weight was 136 pounds; her weight at time of delivery was 172 pounds. The abdominal musculature was very relaxed. The uterus was large and rotated clockwise 90 degrees. The round ligament was felt coursing across the abdomen. The patient had been having strong but ineffectual contractions. Following manual detorsion of the uterus and application of an abdominal binder to hold the uterus in position, labor

progressed quickly and an uneventful delivery of a living 11 pound, 4 ounce female infant ensued. The uterus was explored and was found to be thin and intact. No leiomyomas were felt.

Comment

In our review of the literature we found an additional 2 cases^{2, 5} not included in the report of Nesbitt and Corner.

We feel that torsion of the pregnant uterus is a more common entity than reported but, because of lack of reporting or lack of observation it has been neglected. We feel that its importance is greater now because of the increased tendency toward the transverse incision in cesarean section. If one is not aware of the possibility of torsion and is not cautious, the uterine artery may be severed with this type of incision.

Summary

Three new cases of axial torsion of the gravid uterus are presented. One was diagnosed and treated without benefit of laparotomy.

Addendum. Since this article was written, we have treated a fourth patient with torsion of a pregnant uterus. The patient was a 30-year-old gravida vi, para ii, who had had 3 abortions and who had had a previous right oophorectomy. She was seen at term with ruptured membranes. The fetus was in a transverse lie position. After a 12 hour nonprogressive labor, a low cervical longitudinal cesarean section was performed. The uterus was noted to be rotated 90 degrees to the right and covered with marked tortuous varicosities.

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Treatment of tubal pregnancy

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THERE is little disagreement that tubal pregnancy is an acute condition requiring surgical intervention. Over the years, however, the surgical procedure performed has become more conservative in an effort to preserve a maximum of reproductive tissue and reproductive ability. At one time salpingo-oophorectomy was the procedure of choice and subsequently salpingectomy, removing the involved tube with its contained pregnancy.² A further logical continuation of this philosophy would be to preserve the involved tube, especially if there is no evidence of tubal deformity antedating the ectopic pregnancy. Certainly if the cause of tubal pregnancy were uniformly pelvic inflammatory disease then this choice of procedure would be subject to debate, but in 50 per cent of one series,³ the cause of tubal pregnancy was unknown even after pathologic scrutiny of the specimen, and in others only 10.4 per cent and 22 per cent had evidence of previous salpingitis.^{7, 8} In 1958, Tompkins^{5, 6} reported 14 conservative operations performed since June, 1952. At University Hospitals of Cleveland a conservative operation for tubal pregnancy has been performed since July, 1955, when indicated.

Material

From July, 1955, through October, 1958, 107 operations were performed on staff pa-

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tients who had tubal pregnancies. Private patients were excluded from the report because of difficulty in follow-up. Of these 107 patients 37 had salpingectomies, 17 salpingo-oophorectomies, 1 hysterectomy, and 3 bilateral salpingectomies. Forty-nine had a salpingotomy and salpingoplasty.

Of the 49 patients undergoing plastic tubal operations, 8 had evidence of pelvic inflammatory disease in the nonpregnant tube. Four patients had had previous ectopic pregnancies treated by salpingectomy or salpingo-oophorectomy. In the salpingectomy group of patients, 9 had had evidence of old pelvic inflammatory disease and 2 had had previous ectopic pregnancies.

A survey of the operative notes on patients who did not have the conservative operations showed the reasons for performing a salpingectomy or salpingo-oophorectomy or hysterectomy were that bleeding could not be controlled by other means, that there was pelvic inflammatory disease present and a healthy tube could not be reconstructed, or that the patient had her family and there was no reason to preserve fertility. In some instances there was no reason given for removing the tube.

Method

The operative procedure performed was salpingotomy and salpingoplasty. The tube was incised over the pregnancy parallel to the long axis and on the aspect opposite the mesosalpinx. This procedure was varied little no matter what the location of the pregnancy in the tube. The products of conception were shelled out with the finger

and a sponge, and the incision closed with Atraumatic No. 4-0 plain catgut sutures. Occasionally, it was necessary to tie off a vessel in the mesosalpinx leading to the site of implantation in order to control the bleeding. Frequently, a small hematoma filled the tube but it was felt that this was advantageous in keeping the walls of the tube from adhering. Occasionally, some blood dripped slowly from the fimbriated end after repair, but this was never excessive. Plastic repair over polyethylene tubing was never performed in the presence of an ectopic gestation. Some of the salpingoplasties were performed vaginally in cases where salpingoplasty was decided upon and the tubal lesion was readily available.

Postoperatively, there were no immediate complications. There were no surgical deaths and no patients had evidence of continued or recurrent bleeding. Our preferred method of follow-up was a salpingogram with Lipiodol 6 weeks after operation and a Rubin test monthly for 6 months to try to prevent adhesions.

One patient had a postsalpingogram pelvic abscess. This followed the third attempt at salpingograms which the patient had had postoperatively, in an overzealous attempt to demonstrate a patent tube.

Results

Of the 107 patients studied, 58 had the traditional type of operation and 49 had the conservative plastic procedure. Salpingograms were taken from 6 weeks to 18 months following the procedure. Twenty-nine of the 49 patients had salpingograms. Sixteen of these x-ray examinations showed normal tubes, 10 were equivocal, and 3 showed the previously operated tube was definitely closed. This yields a normal salpingogram rate of 55 per cent in those cases followed by x-ray examination. There were 9 subsequent intrauterine pregnancies in 8 patients, a pregnancy rate of 18 per cent, or a corrected rate of 29 per cent since 6 patients were totally lost to follow up. Four of these patients had normal postoperative salpingograms and 4 of the pa-

tients (who accounted for 5 of the pregnancies) were not subjected to x-ray examinations. Twelve patients had normal x-ray findings and no subsequent pregnancies to date. Fig. 1 shows a normal salpingogram. One patient (DT), as reported in detail below, achieved a subsequent intrauterine pregnancy through the repaired tube and then sustained a repeat ectopic in the same tube, being treated with salpingectomy on the second occasion. Another patient (MLC) sustained a repeat ectopic in the same tube, giving a total recurrence rate in the same tube of 2 patients out of 49, or 4.1 per cent, which is a range similar to that reported in other series.^{1, 4}

Case reports

D. T. was a 33-year-old gravida vi, para v, who on Dec. 13, 1955, had a posterior colpotomy, exploratory laparotomy, right salpingotomy and salpingoplasty, and appendectomy for an unruptured right ampullary tubal pregnancy. The last menstrual period was 8 weeks prior to operation. The pathology report confirmed the diagnosis of tubal pregnancy. The right tube was evacuated and the linear incision closed with a single running layer of No. 4-0 plain catgut. Both ovaries appeared normal, but the left Fallopian tube was noted to be bound down to the peritoneum of the posterior cul-de-sac, and no fimbriated end could be identified. The postoperative course was uneventful. Salpingograms 10 weeks postoperatively showed dye in the right tube but with loculation at the fimbriated end and some dye in the left tube, but none in the distal end (Fig. 2).

The patient had a normal intrauterine pregnancy terminated by spontaneous vaginal delivery on March 26, 1957, and complicated only by mild pre-eclampsia and fetal distress due to cord around the neck. She left the hospital on the third postpartum day with her sixth living child.

Her last hospital admission was on July 18, 1958; the last menstrual period was June 13, 1958. She complained of 9 days of intermittent epigastric and right lower quadrant pain. Pelvic examination was unremarkable but colposcopy yielded 20 c.c. of dark blood without clots. Posterior colpotomy and exploratory laparotomy were performed and an unruptured tubal pregnancy of the right tube with swelling the entire



Fig. 1. Salpingogram taken postoperatively after conservative plastic operation for an ectopic pregnancy in the left tube, showing normal configuration and spill.

length of the tube was revealed. The uterus was normal and the left tube was bound down to the posterior pelvic peritoneum. Right salpingectomy was performed.

Pathology report was right ectopic pregnancy and chronic follicular salpingitis.

The patient was placed on penicillin and streptomycin and the subsequent course was uneventful.

M. L. C. was a 29-year-old Negro woman, gravida iv, para ii. On Oct. 28, 1955, she had a left salpingotomy and salpingoplasty. The last menstrual period was 8 weeks prior to operation. She entered the hospital via the emergency room the day of operation with lower abdominal pain and subsequent vascular collapse. Laparotomy revealed 1,500 c.c. of blood in the abdomen with a rent in the entire lateral aspect of the left Fallopian tube which was repaired with No. 2-0 plain catgut.

The postoperative course was uneventful and salpingograms on Jan. 10, 1956, were reported as normal.

She was well until April, 1958, when she underwent another laparotomy for repeat ectopic pregnancy in the left tube. This procedure was carried out at another hospital. She did well postoperatively and had no further gynecologic complaints.



Fig. 2. Postoperative salpingogram on patient who had an ectopic pregnancy with salpingoplasty in the right tube and a closed left tube. She had a subsequent intrauterine pregnancy.

Salpingograms on Dec. 13, 1958, showed a normal right Fallopian tube with good peritoneal spill and a small amount of dye in the left tube.

Comment

We feel that, in view of the percentage of normal salpingograms achieved after salpingoplasty, this procedure should be undertaken more often than it has been previously. Although the group of patients in whom the tube was repaired have not produced more pregnancies than a similar salpingectomy group, this may be due to the relatively short period of time they have been followed, and it is felt that the preservation of reproductive potential made possible by leaving the tube in the patient warrants the small risk of repeat ectopic in the same tube (2 cases out of 49 with no deaths).

The rate of normal salpingogram following salpingoplasty may be even better than these figures above would indicate. What is important is the achievement of one intrauterine pregnancy and full-term living child, the result of the conception through a repaired tube (DT) the other tube being

closed by x-ray and gross examination at both laparotomies. This pregnancy would have been impossible had salpingectomy rather than salpingoplasty been elected. Therefore, in cases where there is an indication to retain all the reproductive ability possible, where there is no deforming pelvic inflammatory disease, where the fimbria are healthy and bleeding can be controlled, there is reason to perform salpingotomy and salpingoplasty.

Summary and conclusions

1. Reasons for considering plastic repair of a tube involved by ectopic pregnancy are

presented with evidence that the conservative procedure is increasing in frequency. The indications for carrying out a repair, rather than removal of the tube, together with the technique are presented.

2. One hundred and seven cases of tubal pregnancy are reviewed, 58 treated by surgical removal of the involved tube and 49 treated by salpingotomy and salpingoplasty.

3. Two cases of repeat ectopic pregnancy in the same tube are presented.

4. It could be demonstrated that at least one of the pregnancies achieved subsequent to salpingoplasty could not have occurred had salpingectomy been the initial therapy.

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Significance of tubal pregnancy in the reproductive life of women

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TWELVE hundred and seven cases of extrauterine pregnancy were operated on in the Gynaecological Clinic of the University of Zagreb from 1940 to 1958. This gave a relative frequency of one extrauterine pregnancy in 45 term deliveries (2.2 per cent) or one in 11 miscarriages (8.9 per cent). Thus, there has been one extrauterine pregnancy in every 64 obstetrical cases (1.6 per cent). One ectopic pregnancy occurred in each 90 patients of all treated in the Obstetrical and Gynaecological Department during the last 19 years. Each seventh laparotomy during this time was for extrauterine pregnancy.

In more than 99 per cent of the extrauterine pregnancies, we were concerned with tubal pregnancy, hence our analysis is concerned almost entirely with this condition.

Sterility is known to be common following the radical treatment of tubal pregnancy.^{1-4, 11, 12, 16, 20-22} The radical treatment of tubal pregnancy is understood to mean salpingectomy as well as more extensive operations. The percentage of sterility following such treatment has been reported to range from 54 to 88 per cent, according to the records of the world literature.^{2, 4, 11, 16, 20-22} According to Lecene,¹⁴ the average figure for sterility after the surgical management of ectopic pregnancies is 70 per cent.

Questionnaires were sent to 300 women under the age of 35 operated upon in our

Clinic from 1950 to 1955. Answers have been obtained from 114. Pregnancy occurred in 42 patients (36.9 per cent) following salpingectomy. Of these, 22 women (19.3 per cent) were delivered at term, 10 (8.8 per cent) miscarried, and in 10 there was recurrence of extrauterine pregnancy. Therefore, after such operations for ectopic pregnancy, 72 women (63.1 per cent) have never again become pregnant. According to Roux and Marchal²² the percentage of sterility in women whose first pregnancy is a tubal one amounts to 91.5 per cent.

The significance of tubal pregnancy in the procreative life of women has been worked out in a statistical review of all 1,207 cases. Special attention has been given to (a) the age of the patient, (b) the total pregnancies prior to the tubal pregnancy, (c) the total number of recurrent tubal pregnancies, and (d) the pregnancies prior to the recurrent tubal pregnancy. The statistical data obtained have been amplified by study of the records of all cases of tubal pregnancies operated upon in nine gynaecological departments in our Republic.²⁶ We have obtained data on the method of treatment in 1,960 cases, on the age of the patients in 756 cases, and on the number of pregnancies prior to tubal pregnancy in 1,237 cases.

Age of patients with tubal pregnancies

According to the data in Table I, tubal pregnancy is a condition occurring most frequently in patients between the ages of 21 and 35 (76.9 per cent). The frequency of this condition in women above the age

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of 35 amounts to 21.9 per cent and under the age of 20 to 1.2 per cent. Fitzgerald and Brewer,⁸ in an analysis of 500 cases of tubal pregnancy, found that three fourths of the cases occur between the ages 20 and 35.

Total pregnancies prior to tubal pregnancy

On the basis of the number of pregnancies prior to the tubal pregnancy, the patients were divided into three groups.

Group I. Women apparently desiring children (Table II). Women who apparently desired further children made up the first group, which was composed of 3 subdivisions.

Subdivision A. Patients in whom the tubal pregnancy was the first pregnancy. The total of such cases is high and amounts to 25 per cent of the total series. The percentage of patients whose ectopic pregnancy was the first pregnancy has been reported by other authors as follows: Gikić,¹⁰ 25 per cent; Sparling,²⁴ 34 per cent; Fiderle and associates,⁶ 36 per cent; Kanajet,¹³ 45.2 per cent; Tasovac and co-workers,²⁷ 25.7 per cent. According to Bret^{3, 4} and Roux and Marchal,²² there is a high probability of permanent sterility in a woman starting her procreative life with a tubal pregnancy. According to the above authors, the possibility of a recurrence in such cases is 1 in 2, and the probability of a later intrauterine pregnancy is only 1 in 10.

Subdivision B. Patients who had had one or more miscarriages but no term pregnancy prior to the ectopic. This amounts to 11.3 per cent, according to our analysis.

Subdivision C. Patients having had one term delivery but no miscarriages prior to tubal pregnancy. This was 18.6 per cent.

The patients of the subdivisions of Group I represent altogether 54.9 per cent of all tubal pregnancies. Those were women the majority of whom had not yet satisfied their wishes with respect to procreation. Radical treatment of their tubal pregnancies may well greatly decrease the chance of their becoming pregnant in the future.

Group II. Borderline group with respect to desire for more children. In the second group there were 12.6 per cent of patients with one delivery prior to tubal pregnancy and in addition at least one miscarriage. This represents a borderline group in which there are women not desiring further pregnancies as well as those anxious to have preserved their faculty for future childbearing because of their only child.

Group III. Group in general satisfied with their established family. In the third group were placed patients who, prior to the tubal pregnancy had been delivered at term two times or more in addition to having had possible miscarriages. The percentage of such patients came to 32.5 per cent in our analysis. These are the women the majority of whom have met their desire for progeny. Consequently, in most of these the need to preserve the capability of conception does not merit practical consideration.

Table I. Ages of patients affected by tubal pregnancies

Age	Tubal pregnancies	
	No.	%
20	14	1.2
21-25	167	13.8
26-30	364	30.2
31-35	397	32.9
36-40	223	18.5
41-45	39	3.2
46	3	0.2
Total	1,207	100.0

Table II. Number of pregnancies prior to tubal pregnancy

Group	Parity	No. of abortions	Tubal pregnancies	
			No.	%
I	0	0	302	25.0
	0	1	136	11.3
	1	0	225	18.6
II	1	1	152	12.6
	2	1	392	32.5
Total			1,207	100.0

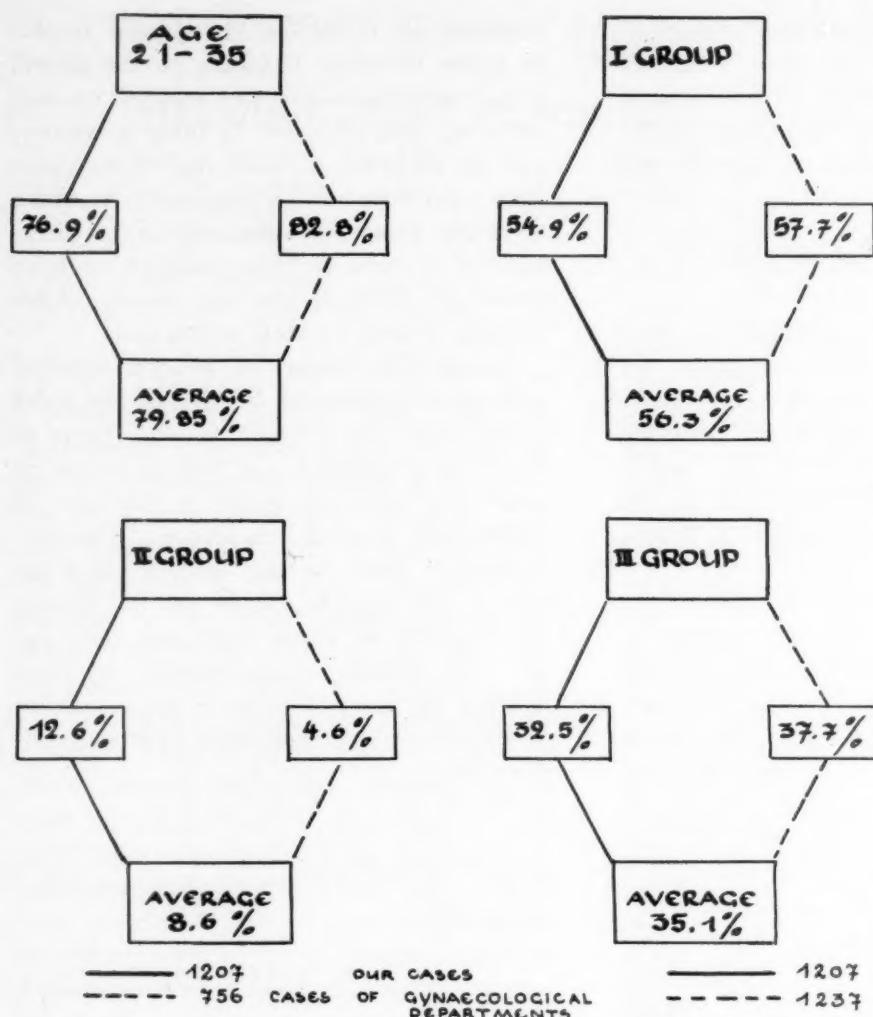


Fig. 1. Diagrammatic demonstration of average age of patients in 1,963 cases of tubal pregnancy (1,207 at our clinic and 756 at other gynecological departments) and average pregnancies prior to tubal pregnancy in 2,444 cases (1,207 at our clinic and 1,237 at other gynecological departments).

Relation of age to prior pregnancies and need for more children

From the data in Fig. 1 it can be seen that of 1,207 women treated at our Clinic and of 756 treated at other gynecological departments, tubal pregnancy occurred in women between the ages of 21 and 35, i.e., during the most fertile phase of life, in 79.85 per cent.

With respect to pregnancies prior to the ectopic one, among the 1,207 patients treated at our Clinic and 1,237 treated in other gynecological departments, 56.3 per cent were in the first group, 8.6 per cent

in the second, and 35.1 per cent in the third. This analysis of 2,444 cases of tubal pregnancy emphasizes the practical importance of tubal pregnancy for later procreation. In 56.3 per cent of all tubal pregnancies the condition interferes with the generative function, particularly in those women in whom the preservation of fertility has the greatest significance. In 8.6 per cent of all patients with tubal pregnancies, we are concerned with women of the second group, who in the majority of cases also wish to preserve their chance of becoming pregnant. In only 35.1 per cent,

patients already having two or more children, is the preservation of fertility of minor importance.

Recurrent tubal pregnancy and the pregnancies prior to it

Of 1,207 patients, 78 (6.5 per cent) were operated upon because of recurrent tubal pregnancy. This percentage fails to show the real incidence, however, because some of these patients were operated upon at our Clinic only following recurrent tubal pregnancy, while others were operated upon for their first tubal pregnancy and it is not possible to establish whether they have been operated upon later somewhere else for a recurrence.

The recurrences reported in answer to our questionnaire amounted to 8.8 per cent. The percentage of recurrences reported in the world literature ranges from 2.38 to 20 per cent.^{11, 20, 22} Bender² stated that a woman becoming pregnant following a tubal pregnancy risks a recurrent tubal pregnancy in 50 per cent of the cases. According to Bender, Roux, and Marchal, the highest percentage of recurrences occurs in women in whom the ectopic was the first pregnancy.

The series of recurrent ectopic pregnancies was made up of 70.6 per cent from the first group, 6.4 per cent from the second group, and 23 per cent from the third group (Table III).

A particularly large number occurred in women whose tubal pregnancy was the first pregnancy (25.7 per cent). Furthermore, in

19.2 per cent of the cases the women concerned had had only miscarriages prior to the recurrent tubal pregnancy. Hence, as a result of the recurrent tubal pregnancy, 44.9 per cent of the patients never had children.

In a further 25.7 per cent the women had had only one delivery and in these women the recurrent tubal pregnancy limited them to one child. In the remaining 24.9 per cent the patients belonged to the second and third groups in which the loss of the chance of becoming pregnant had less practical significance.

Comment

With the historical development of medical science, principles of the operative treatment of extrauterine pregnancy have gradually changed. Former ultraradical operations, e.g., hysterectomy with bilateral salpingectomy, were abandoned long ago. They were replaced first by bilateral salpingo-oophorectomy, then by unilateral salpingo-oophorectomy, later by bilateral salpingectomy, and finally by unilateral salpingectomy only.^{11, 20, 26} In the operative treatment of tubal pregnancy unilateral salpingectomy still represents the method being applied, with rare exceptions, almost routinely at gynecological departments all over the world. We consider salpingectomy, as well as more extensive operation for tubal pregnancy, as radical.

Under conservative operative treatment of tubal pregnancy we have grouped all those plastic operative interventions which enable (1) the preservation of the whole oviduct, (2) the retention of the remaining still healthy part of the tube, and (3) those interventions enabling pregnancy even following removal of both oviducts (transplantation of the ovary according to Estes or Tuffier-Köhler). Caffier,⁵ Gauss,⁹ Funck-Brentano, Bayle, and Palmer,^{7, 19} Lork,¹⁵ Ludwig,¹⁷ Matthaei,¹⁸ Seguy,²³ Szendi,²⁵ Thompkins,²⁸ and others have devoted considerable attention to conservative operative treatment of tubal pregnancy. Our classification of all kinds of conservative

Table III. Distribution of patients affected by recurrent tubal pregnancies

Group	Parity	No. of abortions	Recurrent tubal pregnancies		%
			No.	%	
I	0	0	20	25.7	70.6
	0	1	15	19.2	
	1	0	20	25.7	
II	1	1	5	6.4	29.4
III	2	1	18	23.0	
Total			78	100.0	

operative interventions, indications, and contraindications for such a treatment, as well as our experience with these operations, will be demonstrated in another paper.

Of 1,100 cases of tubal pregnancy operated upon in our Clinic from 1940 to 1957, 1,028 (90.5 per cent) were radically treated. In 105 cases (9.5 per cent) one of the conservative operations was performed either on the affected or on the other oviduct. In three cases of recurrent tubal pregnancy, transplantation of the oviduct utilizing the Estes method was undertaken on request of the patient.

The data from the other gynecological departments demonstrate that in 1,960 cases the percentage of tubal pregnancies treated by conservative operation ranged from 0 to 10.7 per cent, with an average of 4.04 per cent. In the grand total of 3,060 cases of tubal pregnancy, 93.77 per cent were treated radically, while conservative treatment was carried out in only 6.27 per cent.

Medical science now offers facilities that have only recently become available. These should be applied to the problem of tubal pregnancy, a condition jeopardizing the function of reproduction in the most fertile period of the woman's life. The present almost universal use of radical treatment (in our country, 93.77 per cent) corresponds neither with our current views on the importance of fertility in women nor with our real facilities for the care of women affected by tubal pregnancy.

Conclusions

1. Sterility following radically treated tubal pregnancy amounts to 63.1 per cent according to our statistical review.

2. The majority of tubal pregnancies occur during the most fertile phase of a woman's productive life, 79.85 per cent being in women between the ages of 21 and 35.

3. Of all tubal pregnancies, 53.6 per cent occur in women who either have never conceived before, have had only miscarriages, or at the most have had only one child. In such cases the question of preserving fertility is of supreme importance.

4. Tubal pregnancy frequently recurs. The world literature indicates the incidence of recurrent tubal pregnancy amounts to 20 per cent. Our own statistics show frequency to be 6.5 per cent in the Clinic or 8.8 per cent according to the answers to our questionnaire.

5. In 70.6 per cent of recurrent tubal pregnancies we are concerned with women whose previous reproductive record leaves them, for the most part, anxious to have their capability of future pregnancy preserved.

6. The current, almost universal practice of radical operation for tubal pregnancy is out of date, since it is consistent neither with the importance of tubal pregnancy in the problem of sterility nor with our present facilities for conservative operative treatment.

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Effect of position changes on the intensity and frequency of uterine contractions during labor

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THE influence of position changes during labor has received little attention from clinicians and investigators. Bösch, Ikle, and Kaser² and Caldeyro-Barcia and associates⁷ mentioned that with the patient in the dorsal position, uterine contractions have a higher frequency and a lower intensity than when the patient lies on her side. Lorand and Pogany⁸ stated that uterine contractions are stronger and more efficient in the supine than in the standing position. According to Williams,⁹ the contractions have a greater intensity and a lower frequency in the sitting position than in the dorsal position.

Material and methods

In the present work, 84 women have been studied, half during oxytocin-induced labor^{3, 6} and the other half during spontaneous

labor. Thirty-nine patients were in prelabor (i.e., before 2 cm. of cervical dilatation), and the remaining 45 were in the first stage of labor. Excluded from the study were patients who underwent rupture of the membranes, vaginal examination, or changes in the infusion rate, or who received medication during the proposed study period. Emotional disturbances were avoided as much as possible.

Uterine activity was measured by continuous recording of the amniotic fluid pressure¹ and was calculated in Montevideo units, as we have described previously.^{4, 5}

Results

Qualitative study. In the great majority of the cases studied, it was found that, when the patient changes from the dorsal position to the side position (right or left), the intensity of uterine contractions increases and their frequency diminishes (Figs. 1, 4, and 5). On the contrary, when the patient changes from the side (right or left) to the dorsal position, opposite modifications occur in uterine contractility; that is, the frequency of uterine contractions increases, whereas their intensity diminishes (Figs. 2 and 3). No

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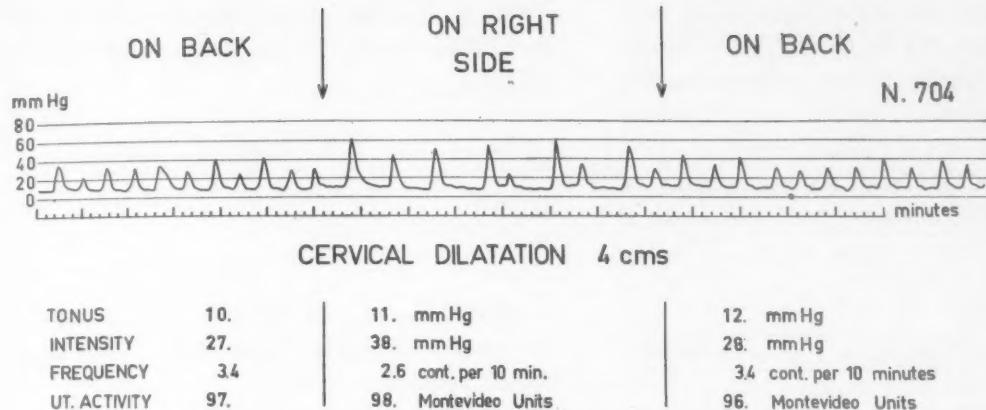


Fig. 1. Full-term pregnancy. Labor induced with intravenous infusion of oxytocin at a rate of 2 mU. per minute. The record of amniotic fluid pressure shows the typical effect of the change of position on uterine contractility. On the bottom, the average values of the tonus, intensity, frequency, and uterine activity are shown for each position.

differences were found in uterine contractility between the right lateral position and the left lateral position (Fig. 5).

The variations of the intensity of the contractions tend to compensate those of the frequency in such a way that the product of both factors, i.e., the uterine activity, is approximately the same when the patient lies on her back or on her side (Figs. 1, 3, 4, and 5). Equal changes occur whether the posture is altered to the right or to the left side.

The changes in uterine contractility occur immediately after the change of position and last for as long as the new position is maintained. The changes of uterine contractility are reproduced every time the patient changes position (Fig. 1).

The law of the position. The facts described above are expressed in the following law: "when the patient lies on the side (right or left), uterine contractions have a greater intensity and a lower frequency than when the patient lies on the back."

The uterine tonus is higher in the dorsal position, possibly because when the patient lies on her side the frequency diminishes and there is thus more time for completing relaxation of the uterus. This factor is particularly significant in cases of too frequent contractions, where the tonus is likely to be elevated (Figs. 3 and 4). Excessive contractility and tonus in the patient who is supine may

be lessened by turning her to the side, which represents a useful clinical application of these observations.

With the patient on her side, the contractions appear to be better coordinated than when the patient is supine. This is particularly true in prelabor (Fig. 5).

Quantitative study. Figs. 6 to 9 show the difference existing in the average values of intensity, frequency, and uterine activity between the dorsal and the lateral position in the 84 cases studied in the present work.

Intensity of the contractions. The average difference found in the mean intensity of the contractions between both positions (7.6 ± 2.1 mm. Hg) is in favor of the lateral posi-

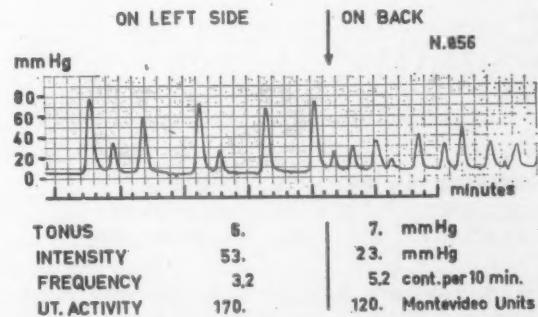


Fig. 2. Full-term pregnancy. Normal spontaneous labor. Cervical dilatation 3 cm. The change of position has a marked effect on uterine contractions.

tion (confidence coefficient higher than 98.4 per cent). This difference is highly significant and indicates a definite relationship between the position change and the variations in the intensity of the contractions.

The average difference in the intensity of the contractions between both positions is

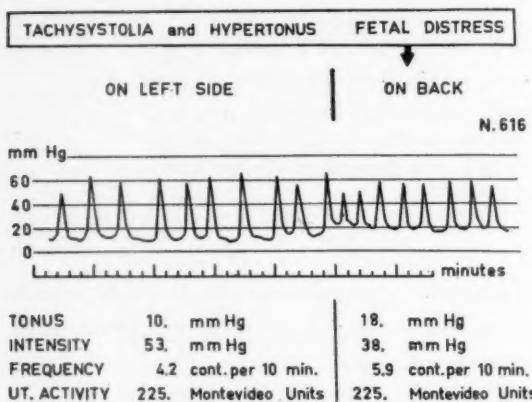


Fig. 3. Full-term pregnancy. Labor was induced with intravenous infusion of oxytocin at the rate of 2 mU. per minute. When the patient changes from the lateral to the dorsal position, the frequency of the contractions increases over 5 per 10 minutes (tachysystolia) and the tonus rises to abnormally high values. Tachysystolia and hypertonicity produce fetal distress. The condition was normalized when the patient returned to the lateral position.

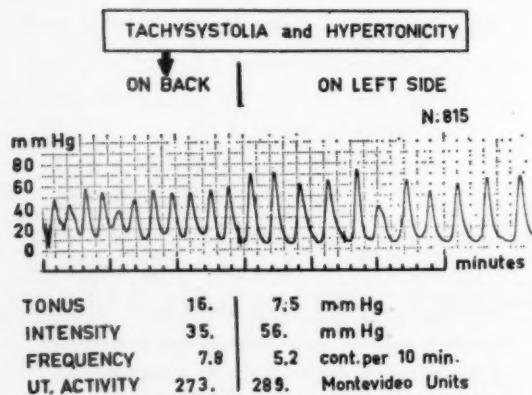


Fig. 4. Full-term pregnancy. Spontaneous labor. Cervical dilatation 6 cm. When the patient lies on her back tachysystolia and hypertonicity are present. When the patient lies on her side, the frequency of the contractions and the tonus descend to normal values.

Table I. Average of the differences between the mean intensities in lateral and dorsal position

	Prelabor	First stage
Spontaneous	11.82 mm. Hg	11.50 mm. Hg
Induced	6.17 mm. Hg	6.54 mm. Hg

Table II. Average of the differences between the mean frequencies obtained in lateral and dorsal position

	Prelabor	First stage
Spontaneous	0.977	1.137
Induced	0.413	0.553

greater in spontaneously beginning labor (11 to 12 mm. Hg) than in labor induced with intravenous infusion of oxytocin (6 to 7 mm. Hg) (Table I).

The lower the intensity of the contractions in the supine position, the greater will be the difference of the intensity between both positions (Figs. 6 to 9).

Frequency of the contractions. The average difference found in the mean frequency of the contractions is 0.7 ± 0.2 contractions per 10 minutes in favor of the lateral position. The confidence coefficient is higher than 99.5 per cent.

The effects of position changes are greater in cases of spontaneous labor than in cases of labor induced with oxytocin infusion (Table II).

The higher the frequency existing in the dorsal position, the greater will be the difference of the frequency of the contractions between both positions (Figs. 6 to 9).

Uterine activity. No significant differences were found in the values of uterine activity between the dorsal and the lateral position (Figs. 6 to 9).

Comparison between prelabor and first stage of labor. The effects of position changes on uterine contractility are of the same order during the prelabor period (Figs. 7 and 9) and during the first stage of labor (Figs. 6 and 8). There is one exception, and this is

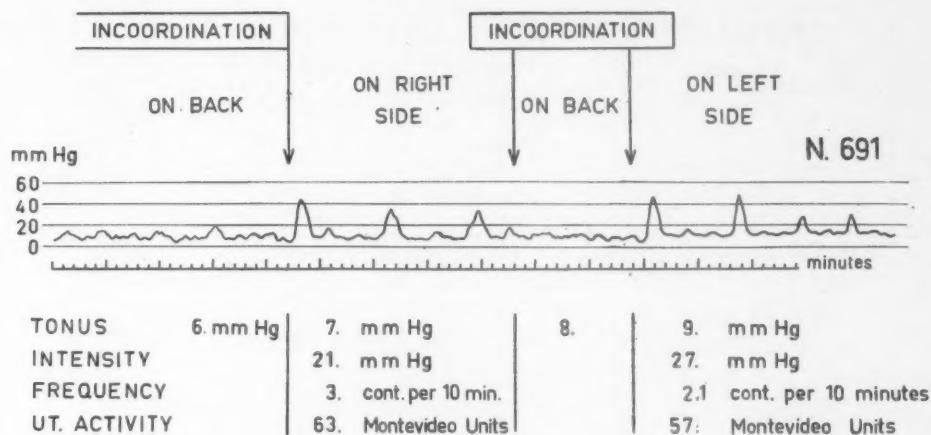


Fig. 5. Full-term pregnancy. Spontaneous labor. Cervical dilatation 1 cm. When the patient lies on her back uterine contractions are small and uncoordinated, whereas, when the patient lies on her side (right or left), the contractions become stronger and their coordination improves.

the frequency of the contractions in spontaneously beginning labor, which is much more influenced by position changes during the first stage than during the prelabor period (Table II).

The changes described were consistent. In prelabor, the changes were present in 93.6 per cent and 87.5 per cent for the frequency and intensity, respectively. In spontaneously beginning labor, they were present in 94 per cent (Table III). In oxytocin-induced labors the changes were present less consistently,

ranging between 66 and 86 per cent, perhaps because of the uterine effects of oxytocin, which tend to mask the effects of postural change.

If the variations in the intensity and in the frequency are considered together for each case, and if only those cases where both factors change in the sense indicated by the law of position are accepted as full positives (Table IV), it is found that the percentage of full positives is somewhat smaller than when the frequency of the contractions and

Table III. Percentage of cases which fulfill the law of position*

	Prelabor			First stage		
	No. of cases	Intensity (%)	Frequency (%)	No. of cases	Intensity (%)	Frequency (%)
Spontaneous	18	87.5	93.6	24	94.4	94.4
Induced	15	86.6	80	27	77.7	66.6

*The intensity and the frequency of the contractions are considered independently.

Table IV. Percentage of cases which fulfill the law of position*

	Prelabor			First stage		
	Positives		Negatives (%)	Positives		Negatives (%)
	Full positives (%)	Weak positives (%)		Full positives (%)	Weak positives (%)	
Spontaneous	87.5	8.3	4.2	88.8	11.2	0
Induced	66.7	20	13.3	59.2	29.7	11.1

*The intensity and the frequency of the contractions are considered jointly.

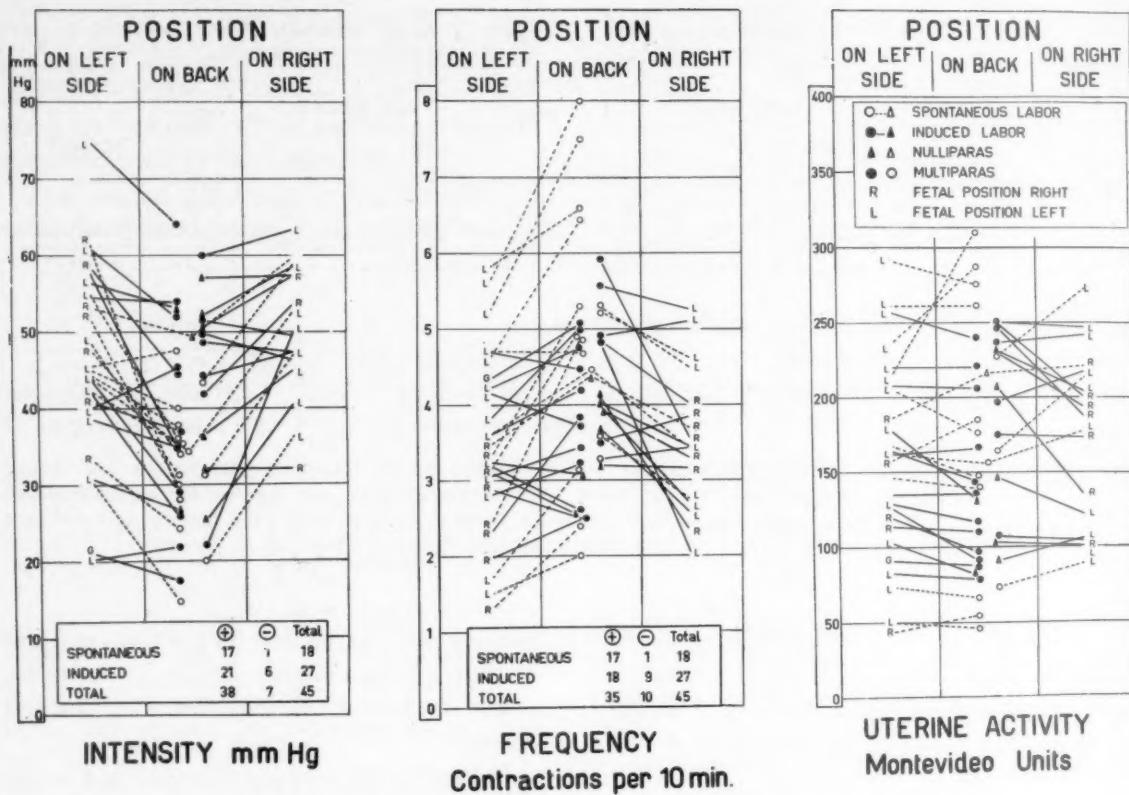


Fig. 6. Absolute values for the intensity, frequency, and uterine activity during the first stage of labor. Each line corresponds to one case and unites the two signs which indicate the values obtained in the dorsal and the lateral position.

the intensity are considered independently.

This difference is due to the fact that in a few cases only one of these factors (the intensity or the frequency) changes in the sense stated by the law, whereas the other factor does not change or shows a very small variation in the opposite sense. These last cases are indicated as weak positives in Table IV.

The above-described changes are not influenced by parity, status of the membranes, or fetal position.

Comment

The mechanisms by which the changes of position of the patient have such important effects on uterine contractility are completely unknown.

The characteristics of the contractions suggest that those produced when the patient lies on her side should be more efficient for the progress of labor than those produced when the patient is on her back.

Summary

The effects of the changes of position of pregnant women on uterine contractility during labor were studied by means of the recording of the pressure of the amniotic fluid in 42 spontaneous labors and in 42 labors induced with oxytocin infusion.

It is found that when the patient lies on her side (right or left), uterine contractions have a stronger intensity and a lower frequency than when the patient lies on her back (law of the position). The effects of the change of position on uterine contractility appear immediately and last for as long as the new position is maintained. The law of position is fulfilled by more than 90 per cent of spontaneous labors and 76 per cent of those induced with oxytocin infusion.

The average variations produced by the change of position are 7.6 mm. Hg for the intensity and 0.7 contractions per 10 minutes for the frequency. The confidence coefficient

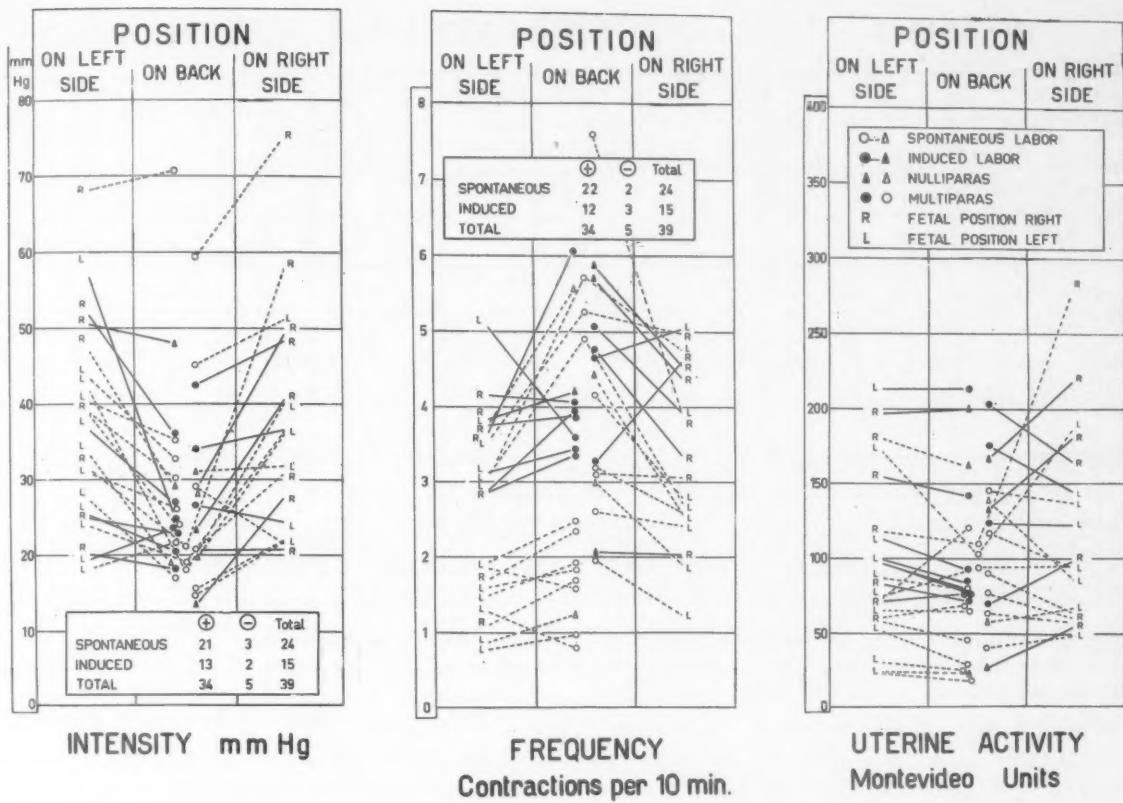


Fig. 7. Absolute values for the intensity, frequency, and uterine activity during the prelabor period. Each line corresponds to one case and unites the two signs which indicate the values obtained in the dorsal and the lateral position.

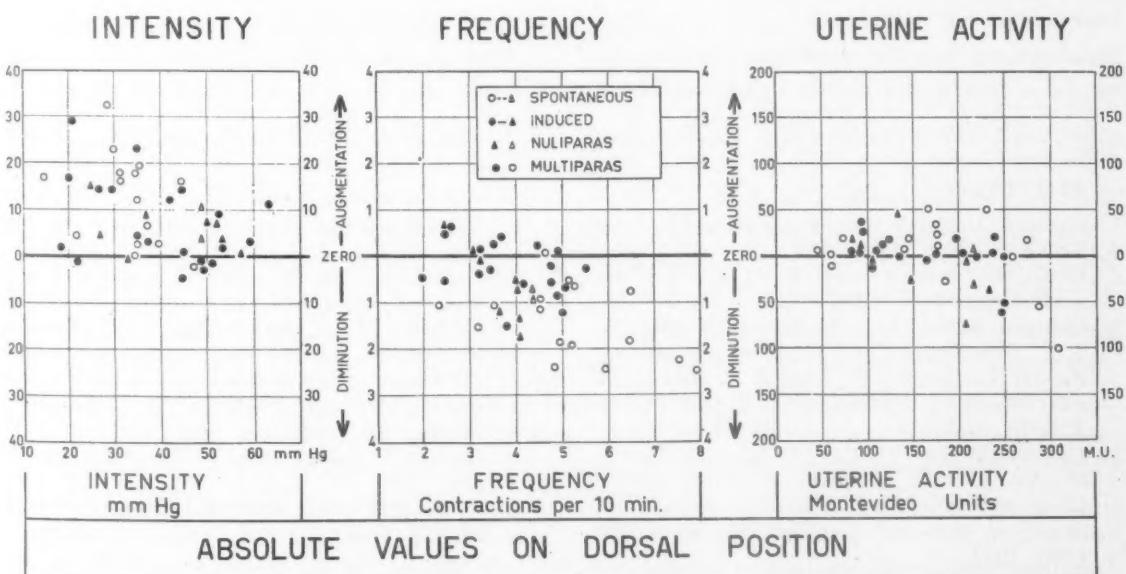


Fig. 8. Differences found between the dorsal and lateral positions in uterine contractility during the first stage. The zero of ordinates corresponds to the absolute values recorded in the dorsal position.

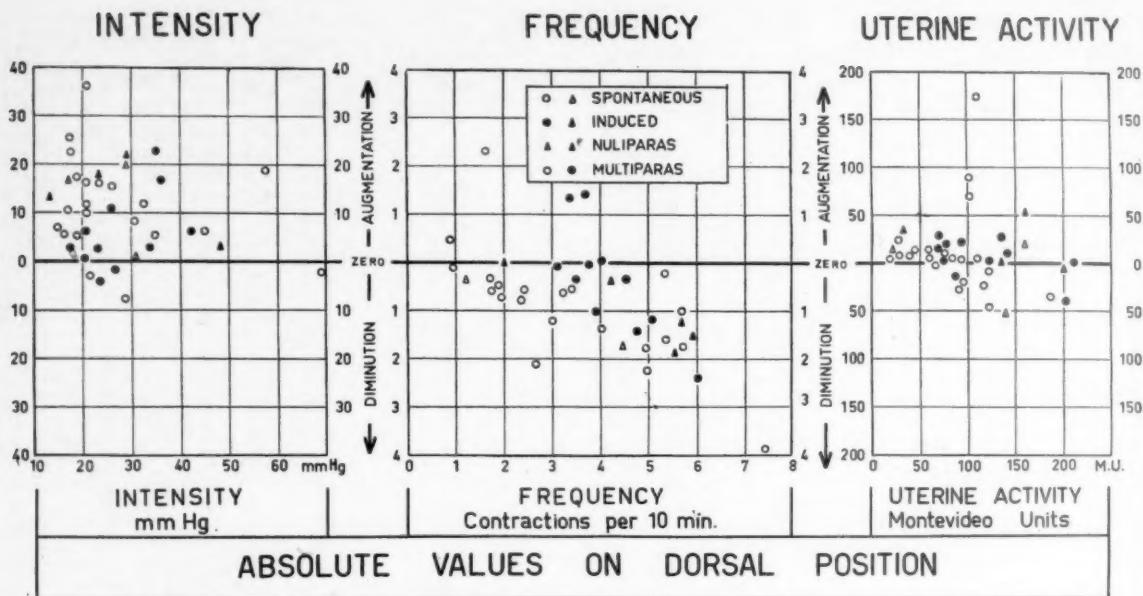


Fig. 9. Differences found between the dorsal and lateral positions in uterine contractility during the prelabor period. The zero of ordinates corresponds to the absolute values recorded in the dorsal position.

is close to 99 per cent. The effects of changes of position are more marked in spontaneous labor than in labor induced with oxytocin infusion. No differences were found in this respect between the prelabor period and the first stage of labor.

Neither parity, the status of the membranes, nor the position of the fetus had any influence on this phenomenon, the mechanism of which is completely unknown. Up to

now, the most interesting clinical application is the treatment of tachysystolia and hypertonicity, which are markedly induced when the patient is changed from the dorsal to the lateral position. The characteristics of the contractions suggest that those produced when the patient lies on her side should be more efficient for the progress of labor than those produced when the patient lies on her back.

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Transverse fetal presentation

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MEDICAL literature has been concerned with transverse fetal presentation since as long ago as the second century A.D.¹ Prior to 1932, contributions were chiefly German and dealt, for the most part, with the optimum time to perform internal version.² In this country interest in the study of the problem dates essentially from Eastman's noteworthy article³ in 1932. The trend in the management of transverse presentation has been ever toward the liberal employment of cesarean section. It is hoped that this report of more recent cases will throw additional light on an important obstetrical problem.

Material

At Charity Hospital of Louisiana in New Orleans from 1953 to 1958, there were 103 infants delivered from true transverse presentation. During this period there was a total of 63,104 deliveries, giving an incidence for transverse presentation of 1:613. This compares favorably with the incidence reported by Montello¹ and that reported by Johnson,² although Aschan and Kinnunen⁴ report 1:208 and Mangone and Kane,⁵ 1:843.

Like most other studies, this series excludes fetuses that converted to vertex or breech spontaneously or were converted by external version prior to the onset of labor or prior to admission. Infants weighing under 1,500 grams and twins are not in-

cluded either. There is unanimity of opinion that internal version and extraction on the second of twins is free of danger. The broad definition of transverse lie—where the long axis of the fetus crosses the long axis of the mother—has been utilized.

Analysis and comment

Race. In Torpin's report⁶ the incidence of transverse presentation was 1:1,090 white deliveries and 1:615 Negro deliveries. In our series the incidence for each of these groups was about the same as the over-all incidence of 1:613. Of our patients, 93 or 90.3 per cent were Negro and 10 or 9.7 per cent were white. The obstetrical clinic population at this hospital is approximately 90 per cent Negro.

Age. Forty-six or 44.7 per cent of the patients were over 30, and 16 or 15.5 per cent were over 35 years old. Considering multiparity as an etiological factor, one would expect a large percentage of older women with a greater number of previous deliveries. Mangone and Kane⁵ reported that 56.9 per cent of their patients were over 30.

Etiology. Much has been written about the etiology of transverse presentation. Nevertheless, this problem remains moot. Often, undoubtedly, a combination of factors is active in causing transverse lie; often the reason is a mystery.

Almost all authors, however, stress the importance of multiparity with accompanying relaxed abdominal and uterine musculature. Of the clinic population at this hospital, 78 per cent have borne one or more

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children. In this series, 99 patients or 96 per cent were para i or more, 73 per cent were para iii or more, and 32 per cent, para vi or more. These figures are somewhat higher than those in other studies.

Likewise, the etiological significance of placenta previa has long been noted. Sixteen or 15.5 per cent of our patients had placenta previa. Webster and Geittmann⁷ reported 25 per cent and Barter and associates,⁸ 20 per cent. In Stevenson's series⁹ of transverse presentations in the last 10 weeks of pregnancy, the placenta was lying in one or the other of the two poles of the uterus in 92.3 per cent of the cases, with placenta previa in 27 per cent. He noted that with polar implantation the amniotic sac takes on a shape more spherical rather than ovoid.

Two of our patients had polyhydramnios and one had leiomyomas obstructing the birth canal. Among other reported causes of transverse lie are contracted pelvis, lumbar scoliosis, ventral hernia, previous uterine suspension, uterine malformation, excess size of fetus, prematurity, fetal death, fetal monstrosity, insertion of Voorhees bag, pelvic kidney, and full bladder or rectum. In this series none of these was important.

It is interesting that 9 or 8.7 per cent of the patients had had previous transverse lie presentations.

Position. In 56 instances position was unspecified. In the remaining cases the acromion was directed toward the right side of the mother 1.2 times as frequently as toward the left; the back was directed anteriorly 2.4 times as often as posteriorly. According to Eastman,¹⁰ the latter figure agrees with that of Schroeder, but he reported the acromion directed toward the

left 2.6 times more frequently than toward the right. Gareis and Ritzenthaler¹¹ found no preponderance of any particular position.

Duration of pregnancy and weight of infant. In 46 patients or 44.7 per cent the gestational period by history was 40 weeks or more; in 87 or 84.5 per cent it was 36 or more weeks. Garber and Ware¹² reported 41.5 per cent of their patients at 40 or more weeks, Mangone and Kane,⁵ 69 per cent over 36 weeks.

Twenty-six or 25.2 per cent of the infants in our series weighed 1,500 to 2,500 grams; 70 or 68 per cent weighed 2,500 to 4,000 grams; 7 or 6.8 per cent weighed over 4,000 grams. As expected, the fetal mortality rate for premature infants (34.6 per cent) was greater than that for the mature (6.5 per cent).

Delay in delivery and fetal mortality. In the reduction of fetal mortality of patients in labor, early recognition of transverse presentation and immediate delivery have been stressed.⁵ Excluding patients not in labor, 48 or 62.3 per cent were delivered within one hour of diagnosis and 64 or 83.1 per cent within 2 hours. The few fetal deaths in this series cannot be correlated with delay in delivery after recognition of presentation. Nonetheless, delivery soon after diagnosis in the majority of cases is thought to be an important aspect of the low total corrected fetal mortality of 7.2 per cent.

Duration of labor and fetal mortality. That fetal mortality in transverse presentation is proportional to the duration of labor is shown in Table I.

Complications. A serious complication of transverse presentation is untimely rupture of the membranes. In Eastman's series³ the

Table I. Relation of fetal mortality to duration of labor

Duration of labor	Cases		Perinatal fetal deaths	Fetal mortality rate
	No.	%		
Nil	15	14.6	1	6.6
1-12 hours	74	71.8	7	9.5
13-24 hours	13	12.6	5	38.5
Over 24 hours	1	1.0	1	100.0

Table II. Method of delivery

Procedure	Number of cases	Per cent
Cesarean section	89	86.4
Classical	40	38.8
Low cervical longitudinal	37	35.9
Low cervical transverse	11	10.7
Extrapерitoneal	1	1.0
Vaginal	14	13.6
Internal version	11	10.6
External version	1	1.0
Embryotomy	1	1.0
Spontaneous evolution	1	1.0
Total	103	100.0

incidence of early rupture was more than 70 per cent. Harris and Epperson¹³ have pointed out that the fetal mortality rate varies directly with the duration of time between rupture of the membranes and delivery. In the 8 cases in our series in which the membranes ruptured 24 or more hours before delivery, the fetal mortality rate was 38.5 per cent. For the 19 patients with ruptured membranes 12 or more hours, the fetal mortality rate was 36.8 per cent. The total uncorrected fetal mortality rate for all 103 cases was 13.6 per cent.

With premature rupture of the membranes Gareis and Ritzenthaler¹¹ found a 52 per cent incidence of cord prolapse and a 55 per cent incidence of prolapse of a fetal part. Their total cord and part prolapse figures were 22.8 per cent and 38 per cent, respectively. Nine or 8.7 per cent of our patients had prolapse of the cord; 18 or 17.5 per cent had prolapse of an arm; 3 or 2.9 per cent had prolapse of a leg. Our comparatively low incidence of prolapse of the cord or of a fetal part is influenced by delivery soon after diagnosis and by rupture of the membranes either at or shortly before delivery in the majority of cases. The fetal mortality rate in cases of prolapse of the cord was 55.5 per cent.

As previously noted, placenta previa complicated 16 or 15.5 per cent of the cases. Low lying placenta was present in 5 patients

or 4.9 per cent, and 3 or 2.9 per cent had abruptio placentae. Twenty-one or 20.4 per cent of the patients had pre-eclampsia, but the over-all incidence of this disease at Charity Hospital is also about 20 per cent. There were 2 cases each of diabetes, syphilis, and leiomyomas.

There was one ruptured uterus, and one patient sustained severe lacerations of the cervix and vagina. Both of these complications were the result of internal version and extraction in neglected cases. The patient with rupture of the uterus underwent hysterectomy. Postpartal atony of the uterus complicating internal version also necessitated hysterectomy in one case. There were 2 hysterectomies for indications incident to cesarean section, one for uncontrollable bleeding and the other for a postoperatively infected endometriocutaneous fistulous tract. The remaining 6 of the 10 hysterectomies were elective at the time of section.

Method of delivery and fetal mortality. Table II shows methods of delivery in this series. Of the patients undergoing cesarean section, 86.5 per cent had either a vertical laparotrachelotomy or a classical section. We prefer a vertical incision. Such incisions can be extended as necessary.

Table III compares this study and others as regards method of delivery and corrected fetal mortality rate (fetuses dead on admission excluded). The comparatively higher cesarean section rate in our more recent series (86.4 per cent) reflects the more widespread use of this method of delivery and is, we believe, largely responsible for the low total corrected fetal mortality rate in this series of 7.2 per cent (uncorrected, 13.6 per cent).

Excluding 3 fetuses dead on admission, our fetal mortality rate according to birth weight in cases of cesarean section is shown in Table IV. For these cases the total corrected fetal mortality rate of 6.9 per cent compares favorably with those of other authors (Table III). This figure would probably be lower had certain complicating factors not been active. Thus, one infant dying soon after cesarean section was born to a pa-

Table III. Comparison of reports as regards method of delivery and fetal mortality (fetal mortality corrected unless specified)

<i>Author</i>	<i>Per cent delivered vaginally</i>	<i>Per cent sectioned</i>	<i>Percentage fetal mortality for vaginal deliveries</i>	<i>Percentage fetal mortality for cases sectioned</i>	<i>Percentage total fetal mortality</i>
Eastman ³	---	---	42.8*	0.0*	30.0*
Novey and Schneider ¹⁴	84.8	15.2	---	---	35.7†
Cole and Delany ¹⁵	53.9	46.1	18.0*	0.0*	8.6*
Johnson ²	91.4	8.6	42.6	25.0	39.5
Harris and Epperson ¹³	---	---	33.3*	7.1	14.3*
Garber and Ware ¹²	75.4	24.6	66.7	7.7	73.8†
Montello ¹	45.3*	54.7*	20.8*†	6.9*†	13.2*†
Gareis and Ritzen-thaler ¹¹	81.0	19.0	---	25.0†	37.7†
Mangone and Kane ⁵	75.4	24.6	51.6	9.5	41.0
Aschan and Kinnunen ⁴	37.7*	62.3*	8.8*	1.1*	4.0*
Holmes ¹⁶	68.6	31.4	33.7	6.0	25.0
Webster and Geitmann ⁷	59.0	41.0	45.2	14.0	28.4
Calkins and Pearce ¹⁷	---	---	32.0	0.0	24.5
Wilson et al. ¹⁸	39.0	61.0	28.0	8.2	14.0
This series	13.6	86.4	10.0	6.9	7.2

*Full-term infants only.

†Uncorrected.

tient with severe diabetes; in another instance, external version with prolapse of the cord and complete abruptio placentae preceded cesarean section and neonatal death.

Excluding 4 fetuses dead on admission, there were only 10 delivered vaginally—8 by internal version and extraction, one following external version, and one by spontaneous evolution. Of these, the only death was that of the premature fetus delivered by spontaneous evolution, giving a corrected fetal mortality rate for vaginal delivery of 10 per cent. This is a low figure compared to those of other series (Table III). Had the number of vaginal deliveries in this series been greater, the fetal mortality rate for vaginal delivery would probably have also been greater.

All 8 patients delivered by internal version and extraction were at essentially complete cervical dilatation when the condition was recognized. Had this not been true, cesarean section probably would have been performed. Although in one case of successful external version the baby was delivered uneventfully as a vertex presentation, the only other case of successful external version was in a patient on whom cesarean section

was performed following prolapse of the cord and who was found to have complete abruptio placentae at operation. In our experience, the infrequent success and the dangers of external version after the onset of labor do not make it a worthwhile procedure. The patient who was delivered of the stillborn fetus by spontaneous evolution precipitated before action could be taken to deliver her otherwise.

Of the 7 fetuses dead on admission, 6 were in so-called neglected cases—i.e., patients with prolonged rupture of membranes, impacted fetus, prolapse of cord and/or a fetal part, and actual or impending amnionitis.

Table IV. Corrected fetal mortality according to weight in cases of cesarean section

<i>Weight (grams)</i>	<i>No. cases</i>	<i>Stillbirths and neonatal deaths</i>	<i>Percentage corrected fetal mortality</i>
1,500-2,500	20	4	20.0
2,500-4,000	61	2	3.3
Over 4,000	5	0	0.0
Total	86	6	6.9

Two of these were delivered by cesarean section, one by section hysterectomy, one by embryotomy, and 2 by internal version and extraction. As noted previously, of the 2 patients undergoing internal version and extraction, one sustained severe lacerations of the cervix and vagina and the other had the only ruptured uterus in the series. The latter required hysterectomy. Most authors now agree that all patients with neglected transverse presentations should undergo cesarean section, with hysterectomy as indicated.

Maternal morbidity and mortality. As discussed earlier, there were 4 nonelective hysterectomies for the following 4 complications: infected endometriocutaneous fistula after cesarean section, uncontrollable bleeding at the time of section, postpartal uterine atony complicating internal version, and rupture of the uterus as a result of internal version and extraction in a neglected case. The other noteworthy feature of maternal morbidity is that 8 patients had postoper-

ative wound dehiscence. There were no maternal deaths in this series.

Summary and conclusions

One hundred and three cases of true transverse presentation among 63,104 deliveries occurring at Charity Hospital of Louisiana from 1953 to 1958 have been analyzed and discussed.

The efficacy of cesarean section in the treatment of transverse presentation is corroborated.

In patients in labor with true transverse presentation of normal viable infants, immediate cesarean section is recommended with one exception. The multipara who is at complete cervical dilatation when first seen may best be delivered by internal version and extraction, provided that the membranes are intact or only recently ruptured, that the uterus is normal and well relaxed, and that there is no fetopelvic disproportion or placenta previa. Neglected cases should be managed by abdominal delivery.

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Prolonged labor—a necessary evil?

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EIGHTEEN to 20 to 36 hours is usually applied as the upper limit of normal labor in primiparas. Figures for the abnormal extension or prolongation of labor in multiparous patients are virtually unavailable. Labor of longer duration than the above figures is called prolonged. For the primipara and the multipara we have adopted 24 hours as a top normal figure.

This analytical study was stimulated by a paper by the senior author.¹ The present paper will have a somewhat broader scope and will emphasize the importance of recognizing certain obstetric features that are potential "troublemakers."

In the 3 year period, 1950 through 1952, 13,214 patients in labor were cared for in the Emanuel Hospital Maternity Department. Among these were 419 patients whose labors were over 24 hours long, an incidence of 3.16 per cent. Of the 419 women, 73 were under 20 years old; 281 from 21 to 30; 42 from 31 to 35; 22 from 36 to 40; and one over 40. It is apparent that this is a normal curve of childbearing through the reproductive years. Only 3 of the patients were non-white. This reflects the relatively low incidence of non-white patients delivered in this hospital.

Three hundred and sixty-six patients were primiparas, 47 had a parity of two, 3 of four, and 6 of more than four.

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In the group with labors from 24 to 30 hours, in duration, there were 237 patients; from 31 to 36 hours, 90 patients; from 37 to 48 hours, 76 patients; and from 49 to 72 hours, 16 patients.

Although a sterile vaginal examination is undeniably important, it was surprising to find that 321 patients were not so examined to evaluate progress. It was also a great surprise to find that this omission was not balanced by x-ray pelvimetry, there being only 33 such studies.

Amniotomy is recognized as an essential adjuvant to labor that is approaching the upper limits of normal, but only 84 patients were offered this assistance. Of these 84 patients, only 11 had membranes artificially ruptured for longer than 12 hours. Twenty-two had ruptured membranes for 6 to 12 hours. Fifty-one were tardily examined and had membranes ruptured within 6 hours of delivery. In 186 patients the membranes had spontaneously ruptured prior to examination. Amniotomy was performed on 149 patients during preparation for delivery.

Although this study is not intended to document the aftermath of prolonged labor, there are several aspects in this regard that must be mentioned. There were no maternal deaths in the study group. Thirty-five mothers had postpartum morbidity by the standard definition, an incidence of 8.36 per cent. The hospital incidence is 2.23 per cent.

Intravenous fluid therapy was considered adequate if the patient received 1,000 c.c. of fluid every 12 hours exclusive of the first 12 hour labor period. Antibiotic therapy was classified as adequate if standard doses were

started and maintained from the second 12 hour labor period. Of the 419 patients with prolonged labor, 298 received inadequate intravenous fluid and antibiotic therapy. Twenty-five (8.4 per cent) of these 298 patients had a morbid postpartum course. Of the remaining 121 patients receiving adequate supportive therapy, however, 10 (8.36 per cent) showed morbidity. With or without prophylactic support, it is apparent that prolonged labor carries with it an inherent risk of morbidity some four times that of normal labor.

There was one intrapartum fetal death (0.2 per cent) in the study group. In the same 3 year hospital period, there were 10 intrapartum deaths of viable fetuses (0.08 per cent). There were 3 neonatal fetal deaths in the study group (0.72 per cent); in the hospital group, there were 22 neonatal fetal deaths (0.17 per cent). The total fetal loss for the study group was 0.95 per cent compared to 0.24 per cent for the hospital group.

The hospital fetal wastage has been corrected to exclude factors unrelated to prolonged labor, i.e., prematurity (and pre-viability), placenta previa, abruptio placentae, prolapsed cord, erythroblastosis fetalis,

and congenital anomalies not compatible with life. As with maternal morbidity, fetal loss in the cases of prolonged labor is four times that in cases of normal labor.

Fifteen babies in the prolonged labor group sustained demonstrable injury or trauma (3.57 per cent). There were 2 cases of facial nerve damage; 5 of cerebral irritability and/or hemorrhage; one of retro-orbital hemorrhage; 4 of bruises and/or lacerations of the head; one of fractured clavicle; and 2 of anoxia referable to the delivery (one of cardiac dilatation).

In the over-all hospital figures, a total of 28 babies sustained demonstrable injury (0.21 per cent); 54 per cent of these injured babies had been subjected to the ordeals of prolonged labor.

The cases of prolonged labor were analyzed for situations that might influence the development of prolonged labor. These were disclosed as follows: (1) inductions of labor; (2) occipitotransverse positions; (3) occipitoposterior positions; (4) breech presentations; (5) other dystocia-provoking positions, (i.e., face, brow, and compound); (6) uterine dysfunction (primary and secondary inertias); (7) absolute fetopelvic dispropor-

Table I

	Hospital group		Prolonged labor group	
	No.	%	No.	%
Total labor patients	13,214	—	419	3.16
Birth trauma or injury	28	0.21	15	3.57
Corrected neonatal and fetal deaths*	32	0.24	4	0.95
Inductions of labor	1,419	61.60†	42‡	59.60†
Occipitoanterior	10,567	77.48	209	50.00
Occipitoposterior	1,864	14.10	140	33.50
Occipitotransverse	409	3.80	34	8.12
Breech	557	4.20	32	7.64
Other abnormal presentations (brow, face, compound)	64	0.48	4	0.95
Uterine dysfunctions				
Primary inertia	*	—	109	26.00
Secondary inertia	*	—	23	5.50
Absolute fetopelvic disproportion (cesarean sections)	220	1.67	57	13.60
Relative fetopelvic disproportion (pelvic arrest-vaginal delivery)	226	1.71	44	12.10
Cervical dystocia (Dührssen incisions)	23	0.17	11	2.60
Abnormality of generative tract	75	0.57	5	1.20
Overdistention of the uterus (polyhydramnios, multiple pregnancy, fetus over 8½ pounds)	2,221	16.82	75	17.90

*See text.

†Per cent successful.

‡Thirty-four patients.

tion; (8) relative fetopelvic disproportion (9) cervical dystocia; (10) abnormalities of the generative tract, especially of the uterus; and (11) overdistention of the uterus, i.e., multiple pregnancies, polyhydramnios, and large babies (over 8½ pounds) (Table I). Prolonged labor is commonly complicated by a multiplicity of these factors.

In 36 patients labor was medicinally accelerated. In 2 of these both fractional dose Pitocin and intravenous Pitocin drip was used. The other 34 patients were equally divided as to one method or the other.

Induction of labor

Thirty-four patients were given 42 inductions of labor. There were 32 medical inductions, 5 surgical (amniotomy) inductions, and 5 medical and surgical inductions. Successful inductions numbered 25 (59.6 per cent). The hospital group revealed an almost identical percentage as well as number of inductions per patient. The incidence of inductions for the hospital and study group is 10 per cent for each.

From these small figures (study group), it is apparent that induction of labor does not seem responsible for leading patients into the state of prolonged labor. However, the exploitation of induction of labor in the presence of other factors that promote prolonged labor impresses us with its injudicious use in many cases.

There were 5 patients with induced labor in whom labor also had to be accelerated. One third of the patients with induced labors exhibited primary inertia. Almost the same number of patients proved to have an occipitoposterior presentation. Labor was induced in one half of the patients with cervical dystocia. It is impossible to assess that induction would produce this or cause the cervix to fail to dilate.

Birth trauma and fetal loss both were increased in pregnancies in which labor was induced. The complexity of factors that could influence these figures and the small number make it impossible to infer a significance, however.

Occipitotransverse position. Although the

great majority of babies enter the superior strait in the occipitotransverse position, the cases so designated in this study deal with this position as it produced dystocia or was associated with it. The incidence of 8.12 per cent was a little more than twice that of the hospital group (3.8 per cent). Inductions of labor were unimportant in this group.

The incidence of uterine dysfunction was slightly increased, predominantly in the cases of secondary uterine inertia. Disproportion, as a result of the occipitotransverse position, was only slightly greater when cesarean section was needed.

Fifty per cent of the cases of occipitotransverse position were associated with pelvic arrest. This is a great increase over hospital and study group figures of 1.71 and 12.1 per cent, respectively. Cervical dystocia is moderately increased in the presence of an occipitotransverse position of the baby. Overdistention of the uterus was not influential in promoting prolonged labor. Pelvic arrest necessitating forceps delivery accounted for both of the injured babies in this group. No babies died.

Occipitoposterior position. To many clinicians and labor nurses, an occipitoposterior position presents a distinct and characteristic labor pattern. The effect on the duration of labor is reflected in Table II. There were

Table II. Occipitoposterior

	No. patients	%
Total cases	140	33.50
Birth trauma or injury	3	2.14
Neonatal and fetal deaths	0	—
Induction of labor	11*	57.10†
Acceleration of labor	19‡	13.50
Uterine dysfunction		
Primary inertia	41	29.20
Secondary inertia	13	9.30
Absolute fetopelvic disproportion (cesarean section)	30	21.40
Relative fetopelvic disproportion (pelvic arrest-vaginal delivery)	15	13.60
Cervical dystocia (Dührssen incisions)	7	5.00
Abnormality of generative tract	1	0.70
Overdistention of uterus	29	20.70

*Fourteen inductions.

†Per cent successful.

‡Four had induction of labor.

three times as many patients with babies in the occipitoposterior position who had prolonged labor as in the hospital figures for all labor patients. One third of all cases of prolonged labor fall into this category.

The incidence of uterine dysfunction (primary and secondary inertia) is slightly higher than in the study group as a whole. It is overshadowed by only two other factors, "absolute disproportion" and "induction of labor." These two situations, however, also have occipitoposterior positions concealed in their figures.

A little more than half of all the patients with accelerated labors had babies in an occipitoposterior position. Four of these 19 also had induced labor.

The incidence of cesarean section is greatly increased. Interestingly, relative disproportion as attested to by the incidence of pelvic arrest was not significantly different. Nevertheless, relative disproportion was considerably greater in this group than in the hospital group.

The need or election to terminate labor with cervical incisions increased twofold in the presence of an occipitoposterior presentation.

Abnormality of the uterus is not a significant factor. Similarly, overdistention of the uterus seemed not to affect materially labor in the presence of an occipitoposterior presentation. Although 3 babies were damaged at birth, the incidence is lower than in the over-all group. No babies died.

Breech presentation. In the study group breech presentation was almost twice that of the hospital figure. This fetal presentation is considered a contraindication to induction of labor, and our hospital staff in general respects this attitude. The incidence of breech presentation with uterine dysfunction (21.8 per cent) is lower than in the study group.

The incidence of cesarean sections in breech presentation is increased over that in the hospital group and in both study groups (breech, 18.7 per cent, and absolute disproportion, 10.5 per cent).

Relative disproportion (6.25 per cent) is lower than the study group incidence, but is

still increased considerably over the hospital figure. Moreover, the incidence of operative vaginal breech deliveries (17) is 65.6 per cent. The over-all hospital incidence for operative breech deliveries is 61.3 per cent.

One third of all the injured babies were breech presentations. The 2 breech deaths were among these 5. These figures are increased sufficiently to re-emphasize the respect that we should have for this fetal position.

Other malpositions (face, brow, and compound). Only 4 cases are in this group of other malpositions and malpresentations, 2 face presentations, one brow, and one compound. Small as this group is, the incidence in the group with prolonged labor (0.95 per cent) is twice the hospital incidence (0.48 per cent).

One patient had a successful induction of labor; 2 had labor accelerated. These latter 2 exhibited primary inertia, once in labor. Dystocia was absolute in 2 and relative disproportion was present in one. One baby was injured at birth.

Uterine dysfunction. Uterine dysfunction (Table III) has been divided into two components: primary uterine inertia is recognized as poor, ineffectual labor contractions from the onset of labor; secondary uterine inertia is identified as poor, ineffectual contractions supervening on a labor pattern that may have been considered adequate in the preceding hours.

Despite our coding system, the hospital incidence of uterine dysfunction is totally inaccurate, either because the attending physicians do not recognize its presence or because they do not code it when it is present. We meticulously reviewed the 419 cases in the study group but the large number of "normal" labor charts was too insurmountable for review. Therefore, comparison with the hospital group is impossible. Uterine dysfunction was added to the study group charts when we felt the diagnosis was warranted. There are some interesting facts to be gleaned from figures in the cases of prolonged labor.

Although there were 132 cases of uterine

Table III. Uterine dysfunctions

	Primary inertia		Secondary inertia	
	No. of patients	%	No. of patients	%
Total cases	109	26.00	23	5.5
Birth trauma or injury	4	3.67	0	-
Neonatal and fetal deaths	1*	0.90	0	-
Induction of labor	12†	66.60‡	0	-
Acceleration of labor	27§	24.80	8	34.8
Occipitoposterior	41	37.60	13	56.6
Occipitotransverse	7	6.40	5	21.7
Breech	6	5.50	1	4.3
Other malpresentations	2	1.80	0	-
Absolute fetopelvic disproportion (cesarean section)	24	22.00	3	13.0
Relative fetopelvic disproportion (pelvic arrest-vaginal delivery)	11	10.10	6	26.1
Cervical dystocia (Dührssen incisions)	7	6.40	2	8.7
Abnormality of generative tract	0	-	1	4.3
Overdistention of the uterus	16	14.70	6	26.1

*Sustained birth trauma.

†Fifteen inductions.

‡Per cent successful.

§Five labors induced.

dysfunction, in only 26.5 per cent of the patients was labor accelerated with Pitocin. Thirty-six patients had amniotomy to enhance labor (39 had to await delivery for the membranes to be ruptured). Of these 36 patients, 19 had the membranes ruptured within 6 hours of delivery. These are impressive figures and indicate to us the lack of attention directed toward the patient entering prolonged labor and the ignorance of or failure to recognize uterine dysfunction during the course of labor.

Twelve (11.0 per cent) of the patients with primary inertia had induction of labor and 5 of these had to have the labor accelerated.

The incidence of occipitoposterior presentations has already been emphasized. Other abnormal positions have an increased frequency with the exclusion of breech presentation. The frequency of cesarean section is almost doubled. Pelvic arrest or relative disproportion is approximately the same.

Cervical dystocia is four times more frequent in the presence of inertia, or as a cause for the inertia. Overdistention of the uterus does not support our suspicion that this would influence the development of uterine dysfunction. Fetal trauma and fetal

loss are not altered by this inadequacy of uterine activity.

Absolute fetopelvic disproportion. To be expected is the sharp increase in the incidence of cesarean sections. This is 8 times that of the hospital group for fetopelvic disproportion (Table IV).

The hospital group was deleted of all indications except cases of cephalopelvic and

Table IV. Absolute fetopelvic disproportion (cesarean section)

	No. patients	%
Total cases	57	13.60
Birth trauma or injury	1	1.75
Neonatal and fetal deaths	2	3.50
Inductions of labor	6*	66.60†
Acceleration of labor	6‡	10.50
Occipitotransverse	5	8.77
Occipitoposterior	30	52.70
Breech	6	10.50
Other malpresentations	2	3.50
Uterine dysfunction		
Primary inertia	24	42.10
Secondary inertia	3	5.27
Abnormality of the generative tract	3	5.27
Overdistention of the uterus	18	31.60

*Six inductions.

†Per cent successful.

‡None induced.

sacropelvic disproportion. These patients all had labor of varying durations up to 24 hours. There were 250 hospital cesarean sections performed after the onset of labor. In 88 per cent, or 220, fetopelvic disproportion was the primary indication. The incidence of cesarean section in the labor group was 1.89 per cent, corrected as above to 1.67 per cent. The study group incidence is 13.6 per cent.

There were 12 patients in whom labor was either induced or accelerated despite the presence of absolute disparity in fetopelvic accommodation. The incidence of occipitoposterior positions was greater than in the over-all study group. Breech and other abnormal fetal attitudes were similarly increased.

The occurrence of primary inertia is significantly greater and should be viewed with concern when present in the labor patient. Secondary inertia was not altered.

No attempt was made to distinguish relative disproportion in the patients undergoing cesarean section. If disproportion was present, it was considered absolute if cesarean section was resorted to (see "relative disproportion" below).

Similarly, if cervical dystocia was present, it was so classified only if Dührssen incisions were made to accomplish delivery. It is our belief that cervical dystocia as a pure entity is rarely an indication for cesarean section, as it then is accompanied by a secondary indication such as true disproportion. Three of the 5 uterine abnormalities necessitated cesarean section.

The preponderance of cases of overdistribution of the uterus consisted of increased fetal size and, therefore, this situation is predictably increased in patients undergoing cesarean section. This is merely a reflection of fetopelvic disproportion.

One baby died just prior to cesarean section and one died 5 minutes after operation, which gives a fetal loss incidence $3\frac{1}{2}$ times that in the study group.

Relative fetopelvic disproportion. Cases were so classified if pelvic arrest was attendant necessitating forceps extraction for de-

Table V. Relative fetopelvic disproportion (pelvic arrest—vaginal delivery)

	No. patients	%
Total cases	44	12.10
Birth trauma or injury	9	20.40
Neonatal and fetal deaths	1*	2.60
Inductions of labor	3†	66.60‡
Acceleration of labor	5§	11.40
Occipitoposterior	17	38.70
Occipitotransverse	17	38.70
Breech	2	4.60
Other malpresentations	1	2.60
Uterine dysfunction		
Primary inertia	11	25.00
Secondary inertia	6	13.60
Cervical dystocia (Dührssen incisions)	3	6.83
Abnormality of the generative tract	0	—
Overdistention of the uterus	6	13.60

*Neonatal death; baby also sustained birth trauma.

†Three inductions.

‡Per cent successful.

§One labor induced.

livery. Twelve per cent were so coded, seven times that in the hospital group.

Labor was either induced or accelerated in 7 patients. One of these babies sustained birth trauma.

We were surprised that the incidence of occipitoposterior position was not increased. However, 3 babies with occipitoposterior presentations sustained injury at birth.

The incidence of breech presentation was slightly increased and both patients in this group had operative vaginal deliveries, i.e., extraction, decomposition, and extraction and/or forceps to the aftercoming head. The one brow delivery was not accompanied by injury or fetal loss.

Secondary inertia was anticipated to be increased and this was borne out. Primary inertia was not changed. Pelvic arrest due to cervical dystocia was increased almost three times. One such case resulted in fetal trauma.

It was unusual to find the incidence of oversized babies (13.6 per cent) actually lower than the study group incidence of 17.9 per cent and the hospital incidence of 16.82 per cent. This is difficult to understand.

Relative disproportion with the necessity

of forceps delivery does carry a greater risk to the baby in so far as birth trauma is concerned. Nine babies were injured (20.4 per cent). One of the babies died, a fetal loss of 2.6 per cent as compared to 0.95 per cent in the study group.

Cervical dystocia. Cases were put in this category if the cervix failed to dilate completely and the patient was delivered vaginally after cervical incisions. The group is very small but has an incidence (2.6 per cent) 15 times the hospital incidence (0.17 per cent). This would be even larger if the hospital cervical incisions were corrected for the occasional emergency Dührssen operation.

As alluded to under occipitoposterior cases, the incidence with cervical dystocia is increased. Cervical dystocia showed a significant rise with occipitotransverse cases as well. Both phases of uterine dysfunction show a significant jump, particularly in primary inertia. Similarly predictable is the increase in pelvic arrest requiring vaginal operative interference in addition to the incisions in the cervix.

Uterine malformation produced an increase in conjunction with cervical dystocia for prolonged labor. Overdistention was not instrumental in this group. The one injured baby was in occipitotransverse position; there was primary inertia and pelvic arrest along with the cervical dystocia.

Abnormality of the generative tract. This consisted of fibroid-tumor involvement in all the cases. These comprise 1.2 per cent of the cases in the group with prolonged labor. These 5 cases make up too small a group to attempt inferential opinions. The concentration of 5 cases in the group with prolonged labor is twice that of the general hospital group, however. Three of the 5 cases displayed occipitoposterior and breech presentation attitudes.

Three had to undergo cesarean section for absolute fetopelvic disproportion—this can hardly be blamed on the degree of uterine disease encountered.

Overdistention of the uterus. Overdistention should have a deleterious effect on the

efficiency and effectiveness of myometrial function. Polyhydramnios, multiple pregnancy, and excessive size of the fetus make up this group. The latter situation was so termed if the baby weighed more than 8½ pounds.

As could be expected, the preponderance of cases fall into this third category, 70 of the 75 cases. All of the 6 cases of patients with polyhydramnios and multiple pregnancy showed a slow increase in distention. There were no cases of acute hydramnios.

Fifty of the oversized babies weighed between 8 pounds, 9 ounces and 9 pounds, 8 ounces; the remaining 20 weighed over 9½ pounds.

The incidence of these three factors as a group in the general hospital was only 1.1 per cent less than in the study cases. It would be reasonable to assume that overdistention of the uterus would alter its physiology in labor, but certainly this dysfunction is not markedly increased in this analysis.

Both occipitotransverse and occipitoposterior positions, as well as other malpresentations, are increased.

Within the prolonged labor group, the uterine dysfunctions are paradoxically opposite to expectations. If broken down into the two previously mentioned types, secondary inertia is increased and this is gratifying. Primary inertia is reduced. Respectively, 26.1 per cent of secondary inertias were complicated by this type of case. About 15 per cent were so disposed in the primary inertia group. For all uterine dysfunctions, 16.8 per cent were complicated by overdistention of the uterus.

Indicated cesarean sections had a sharp increase over the entire study group. Intriguing is the knowledge that if the patient's pelvis is "adequate" for a large baby, relative disproportion played a small role. Either the patient presented an absolute impasse or she had minimal trouble vaginally.

Cervical dystocia and abnormality of the uterus were not influencing factors. Birth trauma was less than in the study group but was greater than the hospital. This is represented by only one baby and he survived.

A fetal loss of 2 is ten times greater than in the hospital figures and three times greater than in the study group. Multiplicity of factors makes it difficult to condemn overdistention, *per se*. Fetal losses in the group with prolonged labor are reviewed in the following case histories.

Case reports

Case 1 (F-36242). Labor was induced in a primiparous patient at 42 weeks. After 30 hours of hard labor a cesarean section was performed for cephalopelvic disproportion and signs of fetal distress. Permission for autopsy was not granted on the stillborn child. Clinically, this case was suggestive of the "postmature" syndrome.

Case 2 (F-12326). A primiparous patient went into spontaneous labor at 40 weeks. At 26 hours of labor, fetal distress prompted intervention. A difficult breech decomposition and extraction was accomplished at full cervical dilatation. The 8 pound, 15 ounce male child died 20 minutes after delivery. Autopsy revealed that the child had a form of erythroblastosis. Whether this would have proved to be fatal or if it was the primary cause of death is conjectural. The delivery manipulations certainly contributed to the outcome.

Case 3 (F-17562). A primiparous patient went into spontaneous labor at 42 weeks. Pelvic arrest was managed by a difficult breech decomposition and extraction. A 10 pound baby was delivered who died shortly after birth. Permission for autopsy was not granted. The difficult delivery could account for this baby's death.

Case 4 (F-18078). This primiparous patient had a successful medical and surgical induction of labor at 41 weeks. The 33 hours of labor reflected primary inertia. She was delivered by cesarean section of an 8 pound, 1 ounce male from the right occipitoanterior position. The baby survived one hour. No autopsy was performed. A necropsy might have shown this death to be attributable to prolonged labor and the attendant circumstances.

Is there a remote sociologic effect to prolonged labor? Prolonged labor would seem to leave a lasting impression on the patient in regard to enlarging her family thereafter. Of the 419 patients, 207 failed to have another baby. Three of these patients lost their babies, and 8 babies were injured.

One hundred and seventy-three of the 207 were primiparas, 32 were para ii to para iv, and 2 were over para iv. These latter 34 could reasonably be excused from seeking another pregnancy.

The majority (117) were between 21 and 30 years. Forty-eight were under 20 years. Thirty-one had cesarean sections and only 43 had spontaneous deliveries.

The 173, or 47.2 per cent, after a 5 year interval, have apparently rejected a subsequent pregnancy.

In the same 3 years that this study was conducted, 395 charts of normal primiparous labor were reviewed. Of these patients, 172 apparently did not again become pregnant (43.55 per cent).

Comment

Prolonged labor is definitely an abnormal feature of pregnancy. This deviation from normality can be a combination of two factors. The one is a set of circumstances that the patient herself exhibits and is inherent in the pregnancy itself. These circumstances have been set forth above. The second is a set of circumstances that is iatrogenic and is the occasion of this analysis.

With the exception of induction of labor and overdistention of the uterus, all the other conditions associated with prolonged labor would seem to play a very significant role.

The increased puerperal morbidity, fetal trauma, and fetal loss are repetitions of what we all have read and acknowledged.

The lasting effect of prolonged labor on the patient and the role it plays in that patient's reproductive zeal should not be minimized.

We feel that a vast number of patients are unceremoniously escorted into this quagmire. We have foregone all mention of how to treat prolonged labor. What is more important is the prevention of prolonged labor by the physician's being aware of potential trouble when satisfactory progress is lacking and heeding certain of the physical findings that have been indicted.

We do not imply that the incidence of

cesarean sections would necessarily be greatly increased. Contrariwise, many of the patients delivering vaginally would do so in less than 24 hours of labor. It would mean that the patients who require a cesarean section would have this operation much earlier.

The accompanying text and tables reveal the complexity that comprises prolonged labor. For this reason, it is almost impossible to single out one factor as the most disastrous.

Uterine dysfunction (notably primary inertia), one of the easier causes to overlook, is one that can be dealt with readily if patient-evaluation is undertaken.

Absolute fetopelvic disproportion should be greatly reduced or even removed from the cases of prolonged labor. Here, pelvic evaluation as to architecture and mensuration must be strongly emphasized.

In relative fetopelvic disproportion the fortitude and judgment of the physician play a most significant role. The decision between vaginal delivery and cesarean section is a difficult one.

Summary

Here is a vignette of an obstetric nightmare: A primipara is admitted for induction of labor. Primary uterine inertia develops,

necessitating acceleration of labor. The baby is discovered to be in the occipitoposterior position. Secondary uterine inertia then sets in. Two alternatives present themselves. Either cervical dystocia and pelvic arrest have to be dealt with, or absolute disproportion becomes apparent and a cesarean section is resorted to.

On the flyleaf of Irving Potter's *The Place of Version in Obstetrics* is the following dedication:

To the "Woman in Travail"
In the reverent hope that
her "hour" may be shortened,
her "anguish" lessened, and
her "joy" made complete.

We have presented the circumstances and conditions that may have a detrimental effect on labor and delivery.

Our appreciation is extended to the Emanuel Hospital Record Librarians for their invaluable assistance and to the physicians of Emanuel Hospital for their permission to review the charts.

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Six years of a family health clinic: some prenatal and pediatric findings

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FOR many years obstetric and pediatric efforts in the United States have been directed against high infant and maternal mortality. With increasingly good obstetric and newborn pediatric care, deaths have decreased to a point where medical sciences can now direct more attention to the prevention of congenital malformations and even to the promotional aspects of optimum health of mother and child.

Prevention of defect and promotion of health are new orientations and result in new approaches to patients. Epidemiologic and laboratory evidence is accumulating on which to base this type of clinical care.

Gregg's¹ classical study of the deleterious fetal effects of rubella occurring early in pregnancy has pointed up the desirability of young girls' acquiring the clinical disease prior to childbearing. Likewise, laboratory

experiments have resulted in the development of principles applicable to man. Ingalls' studies² of hypoxic stress in pregnant mice have demonstrated the role of environment in the production of congenital defects and the critical importance of the stage of pregnancy as well as the duration of stress in determination of numbers and types of anomalies.

Clinical data are needed to confirm principles established in the laboratory, and clinical medicine must make its own contribution to the clarification of the complex field of teratology. A necessary part of such studies is a review of the whole gradient of newborn infants—well babies, babies with minor defects, and babies with major defects—as well as stillbirths and abortions due to developmental abnormality.

The Family Health Clinic of the Boston Lying-in Hospital provided a unique opportunity to study in detail 153 infants from early in pregnancy through at least their first birthday. These children were by and large a sample of the healthy segment of the gradient. However, for full understanding of developmental pathology, the gestational histories and pediatric records of these children are as relevant as those of their less fortunate cohorts.

The Family Health Clinic

This special clinic, administered and staffed by the Children's Medical Center, Boston, by the Harvard School of Public

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The Family Health Clinic was supported in major part by a grant from the Association for the Aid of Crippled Children. Regular members of the staff of the Department of Maternal and Child Health, Harvard School of Public Health, and of the Boston Lying-in Hospital participated. Analyses and preparation of the accumulated data for publication have been made possible by special grants from the Charles H. Hood Dairy Foundation of Boston, and the Milton Fund, Harvard University.

Health, and by the Boston Lying-in Hospital, existed from 1950 to 1956.³ Pregnant women were admitted from the regular outpatient clinics of the Boston Lying-in Hospital provided they were primiparous married women coming early in pregnancy, free of known pathologic conditions, living within a short distance of the clinic, and willing to and interested in giving detailed and frequent information to the staff for research as well as service purposes.

Couples planning a move away from Boston soon after termination of pregnancy were not usually admitted but, because of unexpected family moves, some children were followed for less than one year after birth.

Pregnant women and babies up to 6 months of age were seen in a special clinic of the outpatient department of the Boston Lying-in Hospital, and after 6 months were followed in a special clinic in the Child Health Division of the Children's Medical Center. All deliveries occurred at the Boston Lying-in Hospital.

Except for an occasional change, the same staff members followed the families throughout their association with the Family Health Clinic. These included an obstetrician as over-all director and an obstetric resident who remained with the clinic during the entire 6 year span of operation. Pediatricians, social workers, research nutritionists, public health nurses, and psychiatric consultants also participated. All staff members had the benefit of supervision and consultation from their respective departments at the Harvard School of Public Health, Children's Medical Center, and the Boston Lying-in Hospital.

Acquaintance of staff members with mothers, fathers, children, and often other relatives, begin early in pregnancy. Patients were seen at frequent intervals according to their individual needs and for collection of research data. In general, babies were followed at the usual monthly intervals during the first year of life and at increasingly longer intervals subsequently. Service to patients was integrated and enhanced by

routine pre- and postclinic conferences of staff members, and by frequent casual discussions of patients between professional colleagues. Also, there were occasional scheduled staff conferences with consultant psychiatrists concerning specific families.

In order to provide useful service and research data to all the professional people concerned, records were of extreme importance. A unit record on each family was collected which contained sections on social work, obstetrics, nutrition, pediatrics, nursing, psychiatry, and case conferences. Space remained for the addition of other materials such as pictures and letters. Several of the professions involved used record forms made especially for use in the Family Health Clinic in order to insure the accumulation of specific data. Space was always allotted for the recording of the individual judgments of the professional workers.

The Family Health Clinic mothers

One hundred twenty-six of the total group of 145 mothers registered in the Family Health Clinic are reported on in this paper. Sixteen were omitted because they moved away from Boston or because of voluntary transfer to the regular outpatient department or to a private physician. Two mothers were omitted because they were not followed during pregnancy by the Family Health Clinic staff. One was dropped because she was found not to be pregnant.

These 126 mothers produced 153 live babies and 3 miscarriages. One hundred of the mothers were followed for a single pregnancy (including one set of twins), 24 mothers for 2 pregnancies, one mother for 3 pregnancies, and one for 4 pregnancies.

The socioeconomic characteristics of these women have been reviewed elsewhere.⁴ In general, their income was low, although a large percentage (32 per cent) were college educated.

The average age of the women at the time of pregnancy was 24.2 years with a standard deviation of ± 3.8 years. The average time in pregnancy which they registered in

the clinic was at the third month with a standard deviation of ± 1 month.

Mothers' congenital defects. History of congenital defects in the mothers themselves revealed one with congenital heart disease, Class I, due to intraventricular septal defect, one who had a repaired cleft palate and lip, one with an extra toe, one with 6 supernumerary nipples, and 3 having had repair of pilonidal cysts. Thus, 5.6 per cent of the mothers themselves had congenital anomalies, although none of these were of major clinical significance.

Events of pregnancy. In identifying events during pregnancy which might affect the developing baby, two main categories are considered: those events resulting in chronic stress and those consisting of or resulting from an acute or short-acting stress. Under chronic stress were included chronic systemic disease of the mother (such as heart disease, diabetes, or other endocrine disease), toxemia, pretoxemia, and the gynecologic condition of the patient. Acute stress during pregnancy consisted of accidents, operations, vaginal bleeding, and infection. The time of gestation during which the events occurred and some measure of the magnitude of the stress were noted when possible.

Systemic disease. Twenty-one mothers (16.7 per cent) were classified as having chronic systemic disease. Six (4.8 per cent) suffered from asthma, hay fever, and chronic bronchitis, although none had major attacks during pregnancy. In 10 women (7.9 per cent), questionable thyroid disease was noted. Three of these were being treated with appropriate thyroid medication, and one had had a thyroid adenoma removed. Two women had mild degrees of anemia at 3 and 4 months of gestation. One was physically incapacitated from previous polio. Another mother complained constantly of lower abdominal pain of unknown origin, and one mother had questionable epileptic seizures at 33 and 44 weeks of pregnancy.

Three mothers (2.4 per cent) were diagnosed as having pre-eclampsia, Grade I, and 5 others were considered to be questionably pretoxic.

Gynecologic status. Sixteen mothers, 12.7 per cent of the total group, were diagnosed as having gynecologic disorders. Five gave histories of irregular menses, and 2 had had fertility studies. Five were noted to have retroverted uteri early in pregnancy. Four gave histories of previous abdominal gynecologic operations, and one was diagnosed as having a small fibroid on the anterior uterus.

Also in the above group was a mother (0.8 per cent of the total group) who developed hydramnios. Her child, born with anencephaly and spina bifida, died 45 minutes after delivery.

Bleeding. Twenty-five women, 19.8 per cent of the total group, stated they had bleeding at some time during pregnancy. Three mothers, 2.4 per cent of the total group, aborted at 7 weeks, 18 weeks, and 16 weeks, respectively. Of the remaining 22 mothers who spotted, 14 did so during the first trimester, 4 during the second trimester, and 4 in the third trimester.

Infection. Fifteen women (11.9 per cent of the total group) reported upper respiratory infections during the first 16 weeks of gestation, and one had chickenpox during this time. Although the seasonal distribution of births showed little variation, 90 mothers (71.4 per cent of total group) reported upper respiratory infections between 16 weeks gestation and parturition. Also, in the last 5 months 3 had gastroenteritis, 2 pyelitis, one mumps, one an abscessed vulva, and one a toothache.

Accidents. Seven women (5.6 per cent) gave a history of accidents occurring between 20 and 39 weeks of pregnancy. Three fell down stairs, 2 were in automobile wrecks, and 2 suffered blows to the abdomen. No immediate sequelae were noted other than back ache and uterine contractions in 2 mothers.

Operations. Six mothers (4.8 per cent) had either minor or major operations prior to the termination of pregnancy. Four had tooth extractions, one had an appendectomy, and one a laparotomy at 7 months because of idiopathic abdominal pain.

The Family Health Clinic babies

The 153 babies produced by the 126 Family Health Clinic mothers included 66 males and 87 females. They were followed by pediatricians for an average of 18 months, with a standard deviation of ± 11 months. The average birth weight for females was 7 pounds, 3 ounces and for males 7 pounds, 6 ounces.

As well as reporting on the general health of these children, we also note deviations which might possibly have their origins in prenatal development, some so minor that they could be easily overlooked or, if diagnosed, could be considered in the range of normality.

The majority of deviations considered in this study were noted by the participating pediatricians by the time the infants were 6 months of age. With the exception of 4, all were observed by 12 months of age. Two heart murmurs were not picked up until 18 and 24 months of age, and a diagnosis of heart murmur and strabismus in one child was not recorded until 48 hours of age. It is interesting that of the several hundred observed deviations considered in this paper, only 24 were recorded at the time of the examination of the newborn infant.

Fifty-two cases (34.2 per cent of the total group) of umbilical herniation were recorded, but none required treatment. Twenty-seven (17.8 per cent) children had hemangiomas. Nineteen were faint, non-raised types frequently seen at the nape of the neck. Seven had persistent and/or raised hemangiomas of 1 cm. or less. One child was observed at birth to have a raised hemangioma which involved part of one ear and which increased in size.

Twenty-five (16.4 per cent) children had heart murmurs; 14 were transitory murmurs, 8 persisted as soft Grade I murmurs, and 3 were persistent loud murmurs, louder than Grade I. Of the 3 children with the loud murmurs, 2 were heterozygous twins. The third child in this category weighed 3 pounds, 5 ounces at birth and showed initial slow motor development as well as retro-lental fibroplasia and severe strabismus.

Strabismus was noted on the charts of 22 children. In 12 cases it was a questionable diagnosis, in 8 cases a definite diagnosis (definite strabismus is defined in this clinic as persistent extraocular motor imbalance still evident at 10 months of age when other motor controls such as good sitting balance have been achieved), and in 2 cases a severe strabismus was diagnosed. Ten children (6.6 per cent) thus had a definitive diagnosis of strabismus.

Twenty-one (13.8 per cent) children were noted to have some degree of diastasis recti. Nine cases of hydrocele were observed, one requiring surgical repair.

In a diagnostic category entitled "deviations of the lumbosacral region," 9 children were included. Seven were noted to be dimpled or hirsute in this area. One was stated to have a dimple with polyp and one a pilonidal cyst.

Atopic eczema was observed in 8 children (5.3 per cent). No case was severe enough to require prolonged specific therapy. Seven (4.6 per cent) children were premature, weighing less than 5 pounds, 8 ounces at birth. Six children (3.9 per cent) weighed more than 9 pounds, 8 ounces at birth.

Four cases of inguinal hernia were seen and one baby was diagnosed as having large inguinal rings. Of 3 cases repaired surgically one was bilateral, two unilateral.

Other deviations included ear defects in 3 children, high palate in 3, open parietal sutures in 2, and large heads in 2 (not diagnosed as hydrocephalus). The following anomalies were observed only once: bifid uvula, marked indentation of the upper gum, bifid tongue, lack of enamel on teeth, Meckel's diverticulum (diagnosed at operation), right eye brown and left eye blue, questionable dextrocardia, undescended testicle, and right pupil larger than left.

Family Health Clinic mothers and babies

The deviations from normal just enumerated form the basis on which Family Health Clinic mothers and children were studied in this particular research project. No attempt is made to weight or grade the

Table I. Distribution of 153 Family Health Clinic babies and pregnancies by number of deviations

No. of deviations	No. of babies	No. of pregnancies
0	38	21
1	52	62
2	35	48
3	18	19
4	4	6
5	5	
6	2	
Total	153	156

deviations. Each one has been given the arbitrary score of one.

Table I indicates the distributions of children and mothers by numbers of deviations.

Table II summarizes the pediatric findings on the babies of the 21 Family Health Clinic mothers with negative prenatal histories. None of these babies had deviations of functional importance or of serious clinical significance. In fact, clinically they were very good babies.

Of the 6 mothers each having 4 deviations, 3 (Cases 11, 107, and 111) produced babies in the least good category (Table

III). Of the 3 remaining mothers with 4 deviations each, one had a miscarriage and one produced a child who later developed eczema. The final mother in this category gave birth to a boy with a large head, minimal umbilical hernia, occlusion of the urethra, and markedly bowed legs.

The least good babies in the Family Health Clinic are described in Table III. Actually, all were functionally normal or nearly normal and doing well on clinic follow-up. The maternal prenatal histories of these children are included in Table III. The 19 children, described in the order of listing, included 2 with severe strabismus, 4 with inguinal hernias, one with a large hemangioma requiring x-ray therapy, 2 with persistent loud heart murmurs, one with questionable dextrocardia, 2 with definite lumbosacral abnormalities, 6 premature by weight, and one with Meckel's diverticulum.

Comment

Closing the schism. The Family Health Clinic provided a unique opportunity to study 153 children from early in pregnancy through infancy and often into childhood. Obstetric records were extensive. Of course

Table II. Pediatric findings on babies of the 21 mothers with negative prenatal histories (based on criteria of this study)

No.	Sex	Birth weight	Deviations
12	F	7 pounds, 15 ounces	None
22	F	7	8
28	F	7	1
37	F	6	4
41	F	7	9
46	F	8	13
66	F	7	5
89	M	7	2
91	F	6	12
95	M	9	5
99	F	7	12
108	M	8	0
119	M	8	2
122	M	10	0
124	M	7	4
127	F	8	0
129	F	7	2
135	M	8	6
136	M	8	1
147	M	6	10
153	F	6	7

Table III. The 19 "least good" babies (based on the clinical judgment of Family Health Clinic pediatricians) and their maternal prenatal histories

No.	Baby	No. of deviations (baby)	Prenatal history	No. of deviations (mother)
125	Birth weight, 3 pounds, 5 ounces; high palate; slow development; minimal umbilical hernia; persistent heart murmur; retrosternal fibroplasia and severe strabismus	6	Spotting at 16 and 23 weeks; upper respiratory infection, 23 weeks	3
139	Fixed internal strabismus; minimal umbilical hernia	2	Pre-toxic signs and symptoms; upper respiratory infection, 21 weeks	2
11	Right inguinal hernia	1	Chronic bronchitis; appendectomy, 4 months' gestation; upper respiratory infection, 32 and 38 weeks	4
62	Left inguinal hernia; left hydrocele; transitory murmur; minimal diastasis rectus; minimal umbilical hernia	5	Upper respiratory infection, constant 24-32 weeks; (true knot in cord)	1
107	Bifid tongue; tight frenulum; right inguinal hernia; minimal umbilical hernia	5	Asthmatic bronchitis; thyroid treatment; blow to abdomen, 26 weeks; upper respiratory infection, 18-22 weeks (aureomycin therapy)	4
154	Minimal umbilical hernia; bilateral inguinal hernias	2	Virus infection, 14 weeks (in bed for 3 weeks, lost 22 pounds)	1
111	Spongy hemangioma, left ear; hemangiomas, nostril, eyelids; minimal umbilical hernia	3	Spotting at 2 and 5 months; upper respiratory infection, 6 months (lost weight) and 7 months	4
87*	Persistent systolic murmur	1	Upper respiratory infection, 30 weeks; (?) pre-toxic; poor nutrition	3
88*	Persistent systolic murmur; several small hemangiomas	2		
69	(?) dextrocardia; minimal diastasis rectus; minimal umbilical hernia	3	Constant complaint of lower abdominal pain; previous ectopic pregnancy with suspension and removal of right tube and wedge from right horn of uterus	2
30	Sacral dimple with polyp; persistent heart murmur	2	Irregular menses; under fertility study	1
83	Pilonidal cyst; moderate umbilical hernia	2	Very irregular menses; spotting at 3 and 4 months	3
4	Birth weight, 5 pounds, 4 ounces; faint hemangioma, left eyelid	2	Spotting first 2 months; upper respiratory infection, 36-39 weeks	2
59	Birth weight, 5 pounds; minimal umbilical hernia; alternating strabismus; high palate; minimal diastasis rectus	5	Spotting at 2 months (premature separation of placenta: delivery 1 month before EDC)	1
68	Birth weight, 2 pounds, 12 ounces; anencephaly; spina bifida; absence of pituitary; hypoplasia of adrenals	5	Diarrhea at 24 weeks; hydramnios (delivery at 33 weeks)	2
138	Birth weight, 4 pounds, 14 ounces; (?) left internal strabismus	2	(?) spotting at 19 weeks	1
143	Birth weight; 5 pounds, 4 ounces; nevus, scalp	2	Grade I pre-eclampsia; upper respiratory infection, 23 weeks	2
150	Birth weight, 4 pounds, 12 ounces; transitory strabismus, 9 months	2	Grade I pre-eclampsia	1
53	Meckel's diverticulum; hydrocele; hemangioma in nape of neck; transitory murmur	4	(?) thyroid disturbance; poor nutrition	2

*Twins.

very little could be learned about the physical condition of the baby during the 9 months of intrauterine life, but data were obtained on the condition of the mother (the maternal environment of the fetus) throughout pregnancy, and also about events, such as accidents and illnesses, which affected the mother during this time. In addition, the pediatrician had two or more interviews with one or both parents prior to delivery.

Thus, there was some opportunity to breach the schism between obstetrics and pediatrics, that is, the care of the mother being so completely separated from the care of the child. A continuum of care was further promoted by postclinic staff conferences and by frequent informal discussions between obstetricians and pediatricians.

Teamwork in this way accomplished one of the purposes of the Family Health Clinic: "to study on a coordinated basis the social and psychological, physiological and pathological aspects of pregnancy, birth and early infant care with a view to reducing the present rates of infant mortality and congenital malformations."⁶

Prevention the aim. The latter half of the above statement by the Association for the Aid of Crippled Children seems to reflect the thinking of many workers in maternal and child health and crippled children's programs. Warkany⁷ has stated, "It is clear that children damaged before birth must receive the best of care, that they must be helped to live a life as normal as possible and that their defects must be corrected. But it is equally clear that prevention and not repair must be our aim."

With prevention the aim, the focus of concern becomes the prenatal period. Fetal wastage, congenital malformations, cerebral palsy, disturbed parent-child relationships, and prematurity, which are problems seen in maternal and child health and crippled children's programs have as a common denominator the possibility that optimum care during the prenatal period might prevent or modify their occurrence. Thus, an association which aids crippled children stimulated a clinic service for primarily healthy families.

Healthy mothers. One of the thought-provoking results of work in the Family Health Clinic is the high proportion of variations—often real evidences of pathologic conditions—that close scrutiny of healthy families reveals.

We described the mothers as generally healthy young women with about the usual number of congenital defects themselves. Only one had a serious disease, hydramnios, and produced a baby with anencephaly and spina bifida. Yet we find that 16.7 per cent of these mothers had some chronic systemic disease, 12.7 per cent gynecologic disorders, 19.8 per cent bleeding at some time during pregnancy, 11.9 per cent upper respiratory infection during the first 16 weeks of gestation, and 71.4 per cent upper respiratory infection between 16 weeks and parturition.

Stevenson, Worcester, and Rice,⁵ who reviewed the prenatal histories of 677 congenitally malformed infants born at the Boston Lying-in Hospital between 1930 and 1941, found only 9.9 per cent of the mothers had chronic illnesses, 12.8 per cent gynecologic disorders, 13 per cent prenatal bleeding, and only 1 per cent febrile illness (usually described as upper respiratory infection) during the first trimester. The point to be made is not that the Family Health Clinic mothers have been incorrectly placed near the upper end of the biologic gradient of health-disease. Rather, all parts of the gradient, when subject to close study, reveal great variations among patients, and that the number of deviations found within a group depends largely on the degree of magnification used in the study.

Healthy children. The same principle holds true for the study of children. Although many deviations were recorded, only 19 babies of the total of 153 in the Family Health Clinic were handicapped, or potentially handicapped, in any way by the defects reviewed in this paper (Table III). One of these was a neonatal death.

Stevenson, Worcester, and Rice⁵ found 2.3 per cent of live births at the Boston Lying-in Hospital from 1930 to 1941 were of babies with congenital defects. At the Family

Health Clinic, the anencephalic spina bifida baby is the only one fitting their particular classification of congenital anomalies. Thus, in the small group of Family Health Clinic mothers, the incidence of malformed babies was 0.65 per cent which compares favorably to the figure of Stevenson and associates.

Of the other pediatric deviations noted in this paper, some, such as the eczemas, needed treatment for varying lengths of time, whereas, some, such as the many small umbilical hernias, were of no clinical significance.

Healthy mothers and children. Viewed together, this group of mothers and children lend support to the generally accepted hypothesis that healthy children are associated with healthy pregnancies. Of 156 pregnancies, 3 resulted in miscarriage; one neonatal death occurred, and the remaining 152 children lead essentially normal lives. This hypothesis is also supported by Table II, which lists the minimal pathologic conditions of clinically very good babies with negative maternal prenatal histories.

In spite of rather detailed data no attempt is made here to find statistically significant correlation between prenatal events and subsequent deviations in children. There are many reasons for avoiding cause-and-effect hypotheses. These include a paucity of knowledge about which environmental agents are teratogenic, in what combination, and at what time. Also, it is not known whether prenatal life plays any part in the development of conditions such as eczema.

However, it is of interest to note the maternal prenatal histories of the 19 Family Health Clinic babies considered clinically to be at the lower end of this particular group gradient. Table III proves nothing in itself, but perhaps indicates a number of items to be tested as possible teratologic agents. Some of these are bleeding early in pregnancy, various viral and bacterial infections, and chronic endocrine diseases.

Conclusions

These data on 126 mothers and 153 children support the hypothesis that healthy

children are associated with healthy pregnancies and demonstrate the many variations, some pathologic, which may be found by close study of such groups.

The field of prenatal fetal pathology, long the concern of geneticists and experimental teratologists, has been described as "a no man's land between obstetrics and pediatrics in which progress has not been adequate."⁷ The Family Health Clinic provided a unique opportunity for some joint obstetric and pediatric exploration of this area.

Larger, similarly detailed studies of mothers and children covering the whole gradient of health to disease have been initiated which will test various prenatal events, such as bleeding, infection, and chronic disease, as possible teratologic agents. Much will be learned about the relationship of specific prenatal events to the health status of children.

Summary

Data are presented on 156 pregnancies in 126 women followed over a 6 year period in a Family Health Clinic in Boston, Massachusetts. This research-service clinic collected detailed information from early in pregnancy through at least the child's first year.

The mothers were a select group of young women. Information on congenital defects, systemic disease, gynecologic conditions, accidents, operations, bleeding, and infections is presented.

Of the 156 pregnancies, 3 resulted in miscarriage and one in neonatal death.

Pediatric records of 66 male and 87 female children are reviewed. Major and minor deviations which might possibly originate during prenatal life are reported. Tables are presented describing the babies with negative maternal prenatal histories, the clinically poorest babies, and their maternal prenatal histories.

Prenatal fetal pathology is an area of study which has long been the concern of genetics and experimental teratology. It is also a joint concern of obstetrics and pediatrics.

Similarly detailed studies of mothers and

children along the whole gradient from health to disease have been initiated. These will test various prenatal events as to their possible teratologic effect.

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GYNECOLOGY

Fate of the corpus albicans: a morphologic approach

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THE presence of corpora albicantia in postmenopausal ovaries has been of considerable interest to us. This has prompted a planimetric analysis in which we found no significant quantitative difference with respect to the corpus albicans in ovaries of pre- and postmenopausal women.³ The present paper is a morphologic approach toward further information about the intrinsic structure of the corpus albicans and its relation to the surrounding ovarian stroma.

The formation of the corpus albicans from the corpus luteum has been reviewed^{1, 7, 8} and will not be presented in detail here.

In a morphologic study such as this, we realize that it may be difficult at times to differentiate between a corpus albicans and the hyalinized form of the atretic follicle,

the corpus fibrosum.^{5, 8} We have made serious effort to recognize the smaller size and narrower hyalinized connective tissue zone of the corpus fibrosum.⁸ The fact that the corpus albicans and the corpus fibrosum both present a similar morphologic appearance^{5, 8} does not materially affect our study as we feel they reach the same ultimate fate. In the following paragraphs we shall use the term "corpus albicans" when referring to the hyalinized structures just discussed.

Materials and methods

Thirty cases were collected from our surgical and autopsy files, consisting of 10 each from the following three categories: prepubertal, with an age range of newborn to 10 years; premenopausal, with an age range of 26 to 40 years; and postmenopausal, with an age range of 51 to 86 years. These were picked at random, the only criteria being that no distortion by significant lesions be present, and near sagittal sections only were used.

The slides were stained^{4, 6} with hematoxylin and eosin, Masson's trichrome, Verhoeff's elastic, and Snook's reticulum stains.

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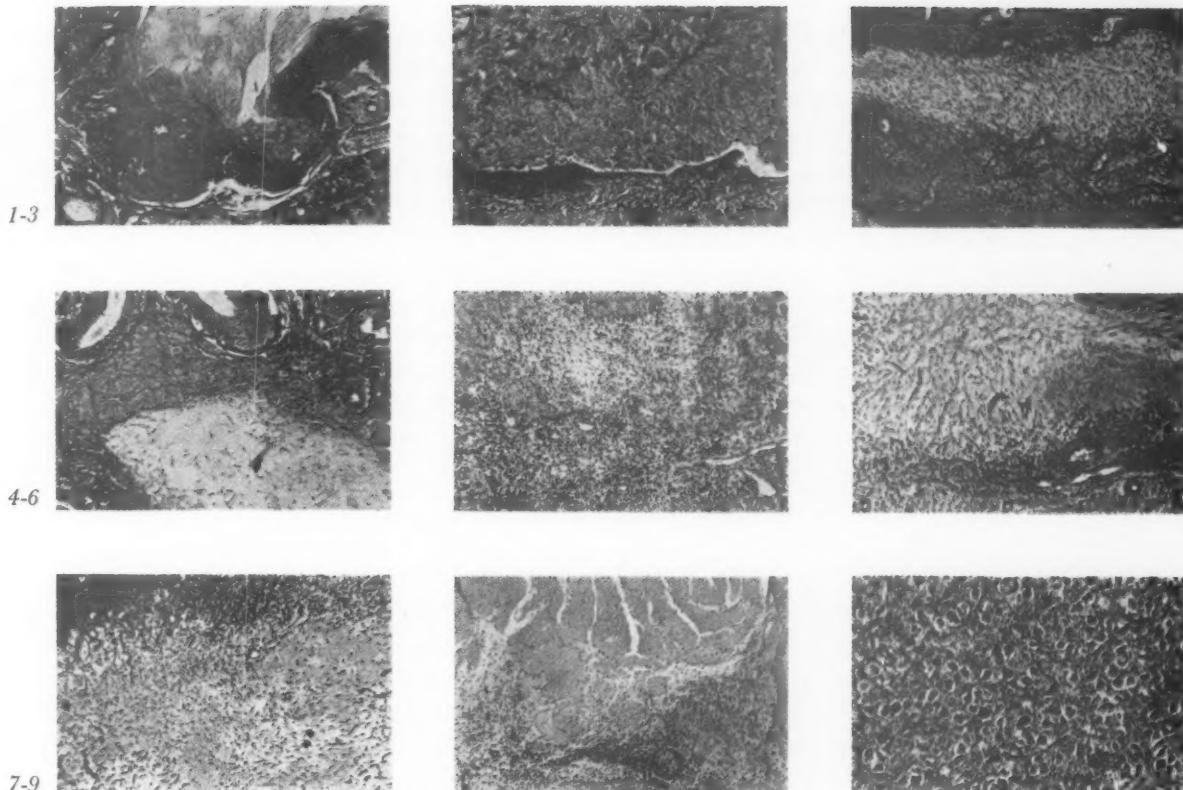


Fig. 1. Oogonia surrounded by stroma in a 1-year-old child. (Masson's trichrome. Original magnification $\times 32$.)

Fig. 2. Fragmentation of the corpus albicans in a 30-year-old woman. (Hematoxylin and eosin. Original magnification $\times 32$.)

Fig. 3. Fibroblasts within corpus albicans in a 30-year-old woman. (Masson's trichrome. Original magnification $\times 32$.)

Fig. 4. Corpus albicans overgrown with fibroblasts in a 30-year-old woman. (Masson trichrome. Original magnification $\times 32$.)

Fig. 5. Fragmentation and fibroblastic overgrowth of corpus albicans in a 29-year-old woman. (Masson's trichrome. Original magnification $\times 32$.)

Fig. 6. Corpus albicans with upper portion having undergone fibroblastic proliferation in a 38-year-old woman. (Masson's trichrome. Original magnification $\times 32$.)

Fig. 7. Complete replacement of corpus albicans by fibroblasts in a 30-year-old woman. (Hematoxylin and eosin. Original magnification $\times 32$.)

Fig. 8. Well-circumscribed corpus albicans with some hyalinization in a 71-year-old woman. (Masson's trichrome. Original magnification $\times 32$.)

Fig. 9. Hyalinization and cystic transformation of corpus albicans in a 54-year-old woman. (Masson's trichrome. Original magnification $\times 32$.)



Each slide was then examined with regard to the following structures: (A) Germinal epithelium, (B) stroma, (C) tunica albuginea, (D) follicular epithelium, (E) blood vessels, (F) hilus cells, (G) theca interna, (H) theca externa, (I) atretic follicles, (J) oogonium and oocytes, (K) theca lutein cells, (L) granulosa lutein cells, (M) fibroblasts, and (N) corpora albicantia.

Results

The first set of slides studied were those of the prepubertal cases. The main objective was to examine ovarian tissue which had never felt the presence of corpora albicantia. The stroma of these infant and fetal ovaries showed none of the effects that the older ones revealed with regard to the stromal reaction to the corpus albicans.

Fig. 1 shows countless oogonia surrounded by stroma. It is significant at this time to note that there is no fibroblastic element seen in this trichrome stain. This group of cases was used as a base line to better evaluate the picture seen in the mature ovaries.

The 10 cases of premenopausal ovaries were examined next. The intrinsic structure of the corpora albicantia showed a consistent staining pattern with the four preparations previously described. We found that the hematoxylin and eosin and the trichrome stains were the most valuable in our study with the elastic and reticulum stains mainly corroborating our findings. The corpora albicantia showed stains of equal intensity throughout all of these premenopausal cases with our techniques. It was noted that the green component of the trichrome stain (light green) became markedly more intense in older, more densely hyalinized corpora albicantia as will be seen later. The first important feature noted in these slides was fragmentation of the corpora albicantia. It could be seen that their structure was interrupted in numerous areas by fibroblastic activity. This can be seen in Fig. 2. Instead of a well-circumscribed structure, well delineated from the surrounding stroma, there is a blending of the corpus albicans at the periphery with the stroma.

In Fig. 3 the fibroblasts are seen deep within the central portion of the corpus albicans. Note the ragged and indistinct periphery of this structure. The trichrome stain shows this process.

Fig. 4 shows an even more advanced stage with the major portion of the corpus albicans overgrown with fibroblastic proliferation. Only a small area of uninvolved corpus albicans structure is seen in the left portion of the photomicrograph.

Fig. 5 shows extensive fragmentation of a corpus albicans with marked fibroblastic overgrowth. There is no semblance of the well-circumscribed corpus albicans in the photomicrograph.

Fig. 6 shows a portion of a corpus albicans in the upper zone that has already undergone fibroblastic involvement, while the lower part of the structure has not yet been subjected to this process.

Fig. 7 reveals complete replacement of a corpus albicans by fibroblasts.

When the postmenopausal cases were studied, a different picture was noted. The corpora albicantia were seen to be well circumscribed in relation to the surrounding stroma. The corpora albicantia were found to be in one structural outline. They were not fragmented and the periphery was clear cut. Hyalinization of the majority of the corpora albicantia was noted. This hyalinization was shown by a more intense light green stain in these particular slides.

Fig. 8 shows a well-circumscribed corpus albicans with some hyalinization. Note the total absence of any fibroblastic activity.

Fig. 9 shows hyalinization and cystic transformation of a corpus albicans. Again, there is no fibroblastic proliferation.

Comment

From our studies, several interesting observations have been made. In the premenopausal ovary the corpus albicans does not appear to be a static structure. It apparently does not remain in the ovary as a white scar but is undergoing modifications. These changes take the form of fragmentation with fibroblastic overgrowth and prolifer-

ation. This transformation was limited to the ovaries of premenopausal women. The postmenopausal ovary apparently is no longer undergoing this type of activity. It would appear that at or near the menopause the stimulus for the corpus albicans replacement by fibroblasts begins to decrease and eventually ceases. Therefore, the last few corpora albicantia formed during the reproductive life of a woman remain and thereby are subjected to the changes of aging. The main feature of this aging process in our material took the form of hyalinization.

As stated earlier, we³ found no significant quantitative difference with respect to the corpora albicantia in ovaries of pre- and postmenopausal women. Hertig² recognized that there were no abrupt changes in the pre- as compared to the early postmenopausal ovaries. There are at least two possibilities concerning the apparent disappearance of many corpora albicantia over the productive life span of the average woman: each corpus luteum does not form a corpus albicans⁶ and/or the corpus albicans undergoes some transformation.

Corner¹⁰ observed that in the rhesus monkey the corpora lutea pass into a phase of prolonged existence termed "corpora

aberrantia" although the ultimate fate of the latter structure was not known. Nothing can be said as yet of the occurrence of similar corpora aberrantia in the human.⁸ We have seen no reference in available literature¹ and no evidence in our studies of regression of a corpus luteum without the usual processes tending toward formation of corpus albicans.

We therefore present our postulation that the corpus albicans in the premenopausal ovary is overgrown by fibroblasts and is thereby assimilated into the ovarian stroma.

Summary

Ten cases each of prepubertal, premenopausal, and postmenopausal ovaries were collected. Slides of these cases were stained with hematoxylin and eosin, Masson's trichrome, Verhoeff's elastic, and Snook's reticulum stains. The slides were then studied with regard to any corpora albicantia present. The postulation that the corpus albicans is resorbed by the stroma of the premenopausal ovary has been presented.

The technical assistance of Mrs. Bette Anderson is gratefully acknowledged.

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Adrenal cortical and Leydig cell nodules in dysgenetic ovaries

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THE syndrome of primary amenorrhea, sexual infantilism, and short stature, along with certain congenital anomalies in an apparent female has been well documented as a definite entity known as Turner's syndrome or gonadal dysgenesis.⁷ We have recently managed a patient with this syndrome by excising abnormally developed gonads and substituting appropriate sex hormones and have discovered histologic structures which shed interesting light upon the embryologic development of the gonad.

Case report

The patient, a 17-year-old apparent female (C. H. No. LSU58-280250), came to Charity Hospital outpatient clinic because she had not menstruated and because she was smaller than her schoolmates. She stated that her voice had always been low-pitched, that she had not grown pubic or axillary hair, and that there was no breast development. Her schoolwork had been average. Her brothers and sisters were apparently normal.

When examined the patient was found to weigh 80 pounds, to be 54½ inches tall, and to have normal blood pressure in both upper and lower extremities. In general, she appeared short but not dwarfed and was normally proportioned with a deep, broad chest. In spite of her age of 17 years she looked like a prepubertal

child. There was no acne. The breasts were infantile and there was no pubic hair. Careful pelvic examination revealed normally formed external genitals, no labial development, small clitoris, small vagina, and undeveloped cervix. No internal genital organs were felt by the examiner. On the left side there was an indirect inguinal hernia.

Cytologic studies of the vagina disclosed basal cells with no estrogen effect and female sex chromatin in about half of the vaginal cells. The urinary FSH level was more than 192 and less than 384 mouse units per 24 hours (high). Urinary 17-ketosteroids measured 8.061 mg. per 24 hours (normal, 5 to 15 mg.). X-ray observations included no epiphyseal retardation, normal function of kidneys with horseshoe configuration, and



Fig. 1. Three cell masses with different composition from the right gonad. *adr*, adrenal cortical nodule; *adr-ley*, combined Leydig cell and adrenal cortical nodule; *ley*, small Leydig cell adenoma; *m*, mesonephric duct.

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small uterus visualized by pneumogynecography. Other laboratory and x-ray examinations gave results within the normal range of values.

A laparotomy was performed for hernia repair, appendectomy, exploration, gonadectomy, and fetal ovarian homotransplant. The presence of horseshoe kidney was confirmed but no other defects were noted besides those of the genitals. An infantile uterus with small uterine tubes occupied its normal position in the pelvis, while at the usual location of the ovaries a whitish yellow ridge of tissue was attached to the posterior upper broad ligament. This streak was smooth and firm and was approximately 2.5 cm. long. It resembled a thick fold of peritoneum. The gonadal ridges were excised. As part of a research project two fetal ovaries were implanted into the rectus sheath.

After a week's observation the patient was discharged from the hospital to be followed in the outpatient clinic.

The gonads were serially sectioned in paraffin and about every fourth slide was stained with hematoxylin and eosin. Microscopically, the two gonads were not alike. The left was made up of typical ovarian cortex surrounding a fibrovascular hilum. No ova or follicles could be found within the cortex. The right gonad could not be identified as an ovary by its microscopic structure. It was composed of fibromuscular tissue liberally penetrated by vessels. There were four features noted on histologic study which were different from any in normal ovary or testis: (1) numerous well-preserved mesonephric tubules and rete clefts were seen; a larger single duct in multiple sections was identified as the mesonephric duct (Fig. 1); (2) throughout

most sections, foci of Leydig cells were clustered around tubules, nerves, and vascular spaces; this represented generalized hyperplasia; (3) several circumscribed agglomerations of these cells made up small adenomas (Fig. 2); in these nodules cells appeared hyperplastic, pale, and large, and they grew in small clusters (Fig. 3), thus differing in detail from the groups of Leydig cells not forming adenomas; (4) two adrenal cortical nodules (Figs. 1, 4, and 5), one of which appeared to be rimmed by and partly composed of Leydig cells (Fig. 5), were noted. In one of the Leydig cell adenomas there was a small central mass of adrenal cortical-type cells, with the typical arrangement of mature adrenal cortex.

Comment

In this instance as in few other comparable cases recorded in medical writings there is graphic demonstration of the intimate association of the gonad and the

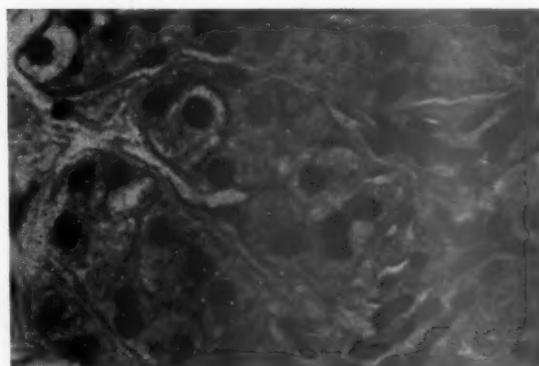


Fig. 3. Hyperplastic hilus cells in adenoma.

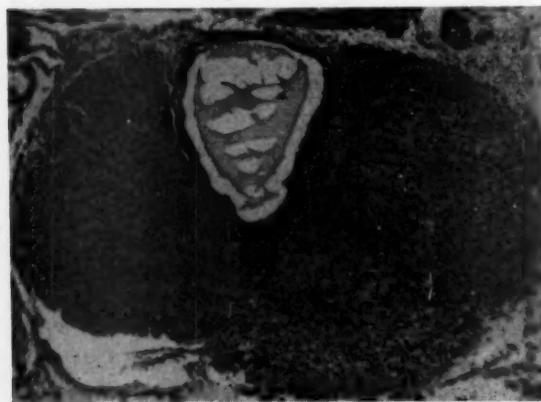


Fig. 2. Hilus cell adenoma surrounding mesonephric tubule.

adrenal gland in their development. Furthermore, the admixture of elements of both interstitial (Leydig) cells of the gonad and cortical cells of the adrenal in this specimen constitutes strong evidence for the common origin of both of these cells. In the present concept of genesis,^{1, 2, 4} the genital cords, cortex, and stroma of the gonads arise from an epithelial mass proliferated from the celomic epithelium and mesenchyme medial to the mesonephric fold in the early embryo. The adrenal cortex originates from a similar mesothelial thickening and is rela-

tively enormous in size as it presses closely against the genital mass. It is no trick at all for some of the cells destined to form adrenal cortex to become incorporated within the mass of similar cells whose future is gonadal. The adrenal cortical nodules seen in this dysgenetic gonad serve only to illustrate the end result of this error of development (Fig. 4). Cortical nodules are commonly found

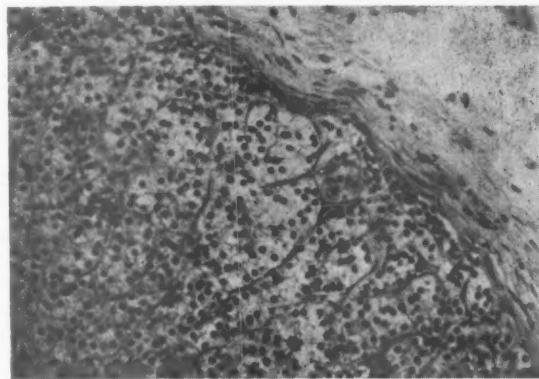


Fig. 4. Adrenal cortical nodule.

in the region of the adrenal gland in less striking manifestations of this same error.⁸

Leydig cells and prominent mesonephric and rete tubules would seem to indicate early organization of the gonad in a masculine direction. It is impossible to determine at what stage in growth of the organ the proliferation of the Leydig cells began, but one reasonable explanation is at hand. Sternberg⁶ has shown that chorionic gonadotropin hormone administered to animals and humans results in hyperplasia of ovarian hilus (Leydig) cells. It may be that pituitary gonadotropin also stimulates growth of these cells. The patient in this study had an elevated FSH level. Although this hormone and pituitary LH may not be elevated until puberty is reached,⁹ the interval of continuous stimulation would still have been long enough to produce the observed hyperplasia. Similarly, it may be possible that long-continued gonadotropin influence may have effected the development of hilus cell

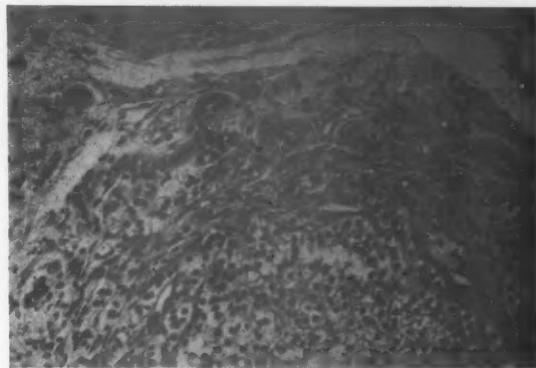


Fig. 5. Nodule made up of adrenal cortical cells in center and Leydig-like cells at periphery.

adenomas. That the masses of Leydig cells did not cause a rise in urinary 17-ketosteroid level is not incongruous, as this finding has not been constant in cases reported.³ Thus, while the persistence of well-developed mesonephric and rete tubules probably represented an error in differentiation of the primitive gonad into ovary, the extreme hyperplasia of Leydig cells probably came later under stimulation of pituitary gonadotropin.

Not so easy to explain is the coexistence of adrenal cortical and Leydig cells in the same nodules. There were two of these. Both had an outer layer of Leydig cells with an inner mass of adrenal cortical cells. It would seem to be inexplicable in any other way than that these two cell types have a common beginning. This hypothesis requires that the celomic epithelium be the progenitor, as the adrenal cortex is unmistakably of that tissue. It is possible that the interstitial cells of both ovary and testis may differentiate from cells of the sex cords (epithelial) instead of from mesenchyme of the gonad.

It is, of course, also possible that the morphologic appearance of both adrenal and Leydig cells is deceiving and that cells in the dysgenetic gonad have inherent potential to grow into shapes resembling each or both of these cell types. However, such a "shotgun" type of explanation is second choice.

Summary

A patient was studied and treated for gonadal dysgenesis. She was outwardly a slightly masculinized female who was found to have female sex chromatin in somatic cells.

The gonads, removed surgically, were unusual in that they contained adrenal cortical nodules, well-preserved mesonephric structures, hyperplastic masses, and aden-

omas of Leydig cells.

It is thought that high pituitary gonadotropin hormone produced the growth of the Leydig cells.

Two nodules contained both Leydig-like and adrenal cortical cells. Common origin of both cell types from the celomic epithelium in the respective primordia would explain this curious combination of elements.

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Correlation between vaginal cytology and endometrial histology

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THIS paper reports a correlative study to ascertain if a specific picture of exfoliative cytology in vaginal smears exists in the presence of certain types of endometrium which may distinguish one from various other types.

Material and method

The cytologic and histologic materials from 365 gynecologic patients admitted to the Vincent Memorial Hospital, Boston, in the years 1954, 1955, and 1956 were used. All the cytologic material was obtained by the vaginal aspiration technique. The endometrial tissue was from either the curettage or hysterectomy specimens. All patients had vaginal smears taken within 48 hours prior to the operation. There was no case of cancer of the uterus or cancer of the vagina.

The histologic findings of the endometrial tissue were reported by the Pathology Department of the Massachusetts General Hospital. Each specimen was routinely examined and classified into one of the four categories: proliferative, secretory, hyperplastic, or atrophic. The vaginal smears were screened in the Vincent Cytology Laboratory and each smear was counted for the three forms of squamous epithelial cells: the superficial,[†] intermediate,[‡] and parabasal[§] cells, with the respective percentages noted.

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[†]Corresponds to the cornified cell in previous terminology.¹

[‡]Corresponds to the precornified cell in previous terminology.

[§]Corresponds to the basal cell in previous terminology.

Results

1. Age of patients. Among the 365 patients, the age ranged from 20 to 82. Patients whose ages were between 40 and 49 constituted the largest single group. Two hundred and fifteen patients were premenopausal and 150 were postmenopausal (Table I).

2. Types of surgical procedure. In 214 patients, the assessment of endometrial histology was based on the tissues obtained from hysterectomy specimens, and in 151 cases it was based on curettage specimens (Table II). No obvious difference was noted between these two types of surgical specimens in the correlation of vaginal smears with the endometrial histology.

3. Indications for operation. In some patients the endometrial tissue was obtained because of primary indications. In other cases, the histologic condition of endometrium was an incidental finding (Table III).

In the group with metromenorrhagia are included the premenopausal patients who complained of metrorrhagia, menorrhagia, or both. None of them was found to have any abnormal pelvic findings. All patients in the group with postmenopausal bleeding had no abnormal pelvic examinations. The distinction between patients with uterine descensus and procidentia depended on whether the cervix was within, or protruding at, the introitus.

4. Vaginal bleeding and endometrium. There were 193 patients who had history of abnormal vaginal bleeding either as one of the chief complaints or as a secondary symptom. Among these patients, 126 were

Table I

<i>Age</i>	<i>Premenopausal</i>	<i>Postmenopausal</i>	<i>Total</i>
20-29	17		17
30-39	58		58
40-49	106	4	110
50-59	34	62	96
60-69		54	54
70-79		30	30
Total	215	150	365

Table II. Types of surgical procedure

<i>Premenopausal</i>	
Hysterectomy	109
Curettage	106
Total	215
<i>Postmenopausal</i>	
Hysterectomy	105
Curettage	45
Total	150

Table III. Indications for operation

Menometrorrhagia	82
Postmenopausal bleeding	44
Cystocele and rectocele	60
Procidentia	37
Descensus	14
Fibroids	30
Cystadenoma of ovary	18
Carcinoma of ovary	13
Dermoid cysts of ovary	15
Simple cysts of ovary	6
Fibroma of ovary	2
Cervical polyp	15
Severe chronic cervicitis	7
Pelvic inflammatory diseases	5
Dysmenorrhea	4
Endometriosis and adenomyosis	3
Abnormal vaginal smears	2
Carcinoma of Fallopian tube	1
Castration for carcinoma of breast	11
Undetermined	6

premenopausal and 67 were postmenopausal (Table IV).

The histology of endometrium in the presence of vaginal bleeding may be of any one of the four types. Among the 126 premenopausal patients who had abnormal bleeding, 50 or 40 per cent were found to have secretory endometrium. Of the 67 patients with postmenopausal bleeding, 46 or 69 per cent showed an atrophic endometrium.

5. Vaginal smears classified according to endometrial histologic findings. Patients were then grouped according to the type of endometrial histology and their vaginal smears were compared (Table V).

Proliferative endometrium. The relative number of exfoliated superficial cells in the vaginal smears varied from patient to patient in those whose endometrium was in the proliferative phase. On the other hand, the number of parabasal cells in the smears was found to be quite uniform. Among 84 patients who had proliferative endometrium, 80 (95 per cent) had only a few parabasal cells (less than 10 per cent) in the vaginal smears.

Secretory endometrium. The relative number of superficial cells in the vaginal smears also varied from patient to patient in the group with secretory endometria. However, the number of parabasal cells in the smears again was found to be uniformly low. Among 94 patients who had secretory endometrium, 92 (98 per cent) had only a few parabasal cells (less than 10 per cent) in the vaginal smears.

Hyperplastic endometrium. The relative number of superficial cells varied again from one patient to another who had hyperplastic endometrium, but not the parabasal cells. Of the 43 patients with endometrial hyperplasia, 41 (96 per cent) had only a few parabasal cells in the smears.

Atrophic endometrium. It is interesting to note that in spite of the atrophic endometrium, superficial cells may still be found in the vaginal smears of some patients. Of the 144 patients with atrophic endometrium, 30 had more than 30 per cent; and 9 had more than 60 per cent of superficial cells in their smears.

Furthermore, the parabasal cells were not invariably present in the vaginal smears when the endometrium was atrophic, since 97 of the 144 patients (67 per cent) had only a few parabasal cells in the smear.

It may be assumed that, based on the findings in endometrial tissue, none of the four histologic types was found to be associated with any specific cytologic pattern to

Table IV. Vaginal bleeding and endometrium

Endometrium	Premeno-pausal		Postmeno-pausal		Total
	Bleeding	No bleeding	Bleeding	No bleeding	
Proliferative	45	29	4	6	84
Secretory	50	44	0	0	94
Hyperplastic	20	3	17	3	43
Atrophic	11	13	46	74	144
Total	126	89	67	83	365

distinguish itself from the others. However, except for the atrophic endometrium, the proliferative, secretory, and hyperplastic types were definitely associated with vaginal smears containing only a few parabasal cells.

6. Expected endometrial histology in specific vaginal smears. If the vaginal smears were grouped according to the relative number of superficial cells, no definite type of

endometrium was found to be associated with any group of smears (Table VI).

However, if the smears were grouped according to the relative number of parabasal cells, one point seems outstanding. Again, let 10 per cent be the border line and let any smear containing more than 10 per cent parabasal cells be regarded as an "atrophic" smear. Then there were 55 patients among the 365 who had "atrophic" smears, and 47 (86 per cent) of them were found to have atrophic endometrium as well.

It seemed that, while the superficial cells in the vaginal smears bore no correlation with the type of endometrium, the majority of patients with "atrophic" smears may also have atrophic endometrium.

Summary and conclusion

A correlative study was conducted in 365 patients to ascertain if a specific cytologic

Table V. Number of patients in 4 types of endometrium and their smear patterns

No. of patients	Type of endometrium	Superficial cells				Parabasal cells			
		Minimum*		Moderate		Advanced		Marked	
		No.	%	No.	%	No.	%	No.	%
84	Proliferative	17	20	25	30	20	23	22	27
94	Secretory	40	43	23	24	21	22	10	11
43	Hyperplastic	5	11	10	23	14	33	14	33
144	Atrophic	73	51	41	28	21	15	9	6
		97	67	10	7	17	12	20	14

*Minimum, 0 to 10 per cent; moderate 11 to 30 per cent; advanced 31 to 60 per cent; marked 60 per cent and up.

Table VI. Number of patients having various smear patterns and their endometrial findings

No. of patients	Smears	Type of endometrium							
		Proliferative		Secretory		Hyperplastic		Atrophic	
No.	No.	%	No.	%	No.	%	No.	%	
<i>Superficial cells</i>									
135	Minimum*	17	13	40	29	5	4	73	54
99	Moderate	25	25	23	23	10	1	41	42
76	Advanced	20	26	21	28	14	8	21	28
55	Marked	22	40	10	18	14	26	9	16
<i>Parabasal cells</i>									
310	Minimum	80	26	92	30	41	13	97	31
16	Moderate	3	19	1	6	2	12	10	63
18	Advanced	1	5	0	0	0	0	17	95
21	Marked	0	—	1	5	0	0	20	95

*Minimum, 0 to 10 per cent; moderate 11 to 30 per cent; advanced 31 to 60 per cent; marked 60 per cent and up.

pattern exists in the presence of a certain type of endometrium which may distinguish it from other types of endometrium.

The superficial cells exfoliated in the vaginal smears showed no apparent correlation with the histology of endometrium. They may be found in varying numbers in vaginal smears with all types of histology, including the atrophic endometrium. Among the patients with atrophic endometrium, 21 per cent had a moderately high and 6 per cent had a very high count of superficial cells in the vaginal smears.

However, the number of parabasal cells in the smears seemed to be a more reliable index

reflecting the activity in the endometrium. In 221 patients who had either a proliferative, secretory, or hyperplastic endometrium, 213 (97 per cent) had only a few parabasal cells in the smears. On the other hand, among patients with an appreciable number of parabasal cells (more than 10 per cent) in the vaginal smears, 86 per cent, of them had atrophic smears as well.

It may be concluded that only the presence of parabasal cells in the vaginal smears is of significance in evaluating the histology of endometrium. When the parabasal cells are present in a considerable number, an atrophic endometrium may be expected.

Endometrial biopsies in the office

Report of 400 cases

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THE uterine curette is one of man's oldest surgical tools. Pre-Christian Greek instruments are almost identical with modern devices for scraping and/or emptying the uterus²⁵ (Fig. 1). About 40 years ago, according to Palmer and associates,¹⁹ Howard Kelly advocated the aspiration of endometrium through a narrow tube. Klingler and Burch¹⁰ in 1932 described a flexible copper tube, perforated at the end and attached to a suction apparatus; with this, they obtained endometrial specimens. In 1935 Randall²⁰ presented a rigid, curved metal tube with a cutting tip for dislodging endometrium. This was the first major modification of the spoons and scrapers of the ancients. Novak¹⁵ in 1935 offered a similar hollow curette, and since then several minor variations of these instruments have been described.^{4, 6, 11, 21, 25, 29} These cannulas with cutting tips have been called "aspiration" curettes. Actually there is no need to aspirate, since the wormlike strips or fragments of endometrium are pushed up into the tube as the cutting tip is drawn across the lining of the uterine cavity. Pressure from a barrel syringe easily expels the tissue into a fixative solution. Randall,²⁰ in his original description of the cannula or tubular curette,

warned against using suction during biopsy lest the tissue be less satisfactory for microscopic study. It is suggested that "cannula curette" is a more accurate designation of the Randall type of instrument than "aspiration curette."

It early became apparent that endometrial samples, adequate for diagnosis of the menstrual phase of the endometrium, could be obtained with the cannula curette. This procedure is now widely employed.^{5, 14, 17, 24} Champ and Pollack² and Rubin²³ each reported the chance finding of two adenocarcinomas of the endometrium biopsies from infertile women. Paalman¹⁸ discovered an asymptomatic widespread endometrial cancer in a 21-year-old infertility patient. Many other such unsuspected cancers of the uterus have undoubtedly been found. In the small literature dealing with endometrial biopsy there are at least 4 reports expressing satisfaction with the wide use of endometrial biopsy for diagnosis: Douglas³ in 1941, 267 biopsies with 3 carcinomas; Williams and Stewart³⁰ in 1947, 200 biopsies with 18 carcinomas; Palmer and associates¹⁹ in 1950, 301 cases with 95 malignancies, and Wall and associates²⁸ in 1954, 445 patients with 95 endometrial cancers. The three latter communications compared the diagnostic accuracy of endometrial biopsies with conventional dilatation and curettage; all reported the two methods equally reliable. Williams and Stewart³⁰ concluded that the chief advantages of endometrial biopsy (immediate acceptance by the patient and economy) "weigh heavily against objections to

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its use, either real or theoretical." Hofmeister,⁸ in work to be published, records 20 endometrial cancers in 3,039 office biopsies; 20 per cent of these patients had malignancies which were entirely unsuspected; 40 per cent of them had "spotted" only once.

Technique of procedure

It is not difficult to use the cannula curette. The vagina is cleansed with an aqueous antiseptic and the cervix exposed with an appropriate speculum. It is often helpful to steady the cervix with a single-toothed tenaculum. A choice of curettes having three different arcs of curve facilitates obtaining adequate samples from uteri with varying degrees of flexion. Whatever discomfort the patient may feel occurs chiefly as the curette (4 mm. in diameter) is passed through the region of the internal os. Recently, it has been noted that a local anesthetic injected (after skin-testing) at the level of the internal os is effective in blocking all or most of the pain. Mengert¹³ at the University of Illinois Clinic has also found this procedure valuable. Rather than merely taking a sample from each quadrant of the endometrium, we try to curette "around the clock." After the procedure is explained and the saving of time and expense pointed out, whatever discomfort the patient feels is generally tolerated without complaint. She is told that there will be some cramping, which is usually gone by the time she leaves the office. After the tissue is obtained, a standard string tampon is inserted, to be removed when the patient reaches home.

It is felt that in a large number of patients in whom one can perform a satisfactory pelvic examination and visualize the cervix one can secure with the cannula curette endometrium adequate for microscopic study. It has been observed that adequate curettings are usually obtained in direct proportion to the patience and gentleness with which one proceeds. In our experience, the use of the cannula curette is seldom more distressing to the patient than the time-honored punch biopsy for the cervix—often less so.

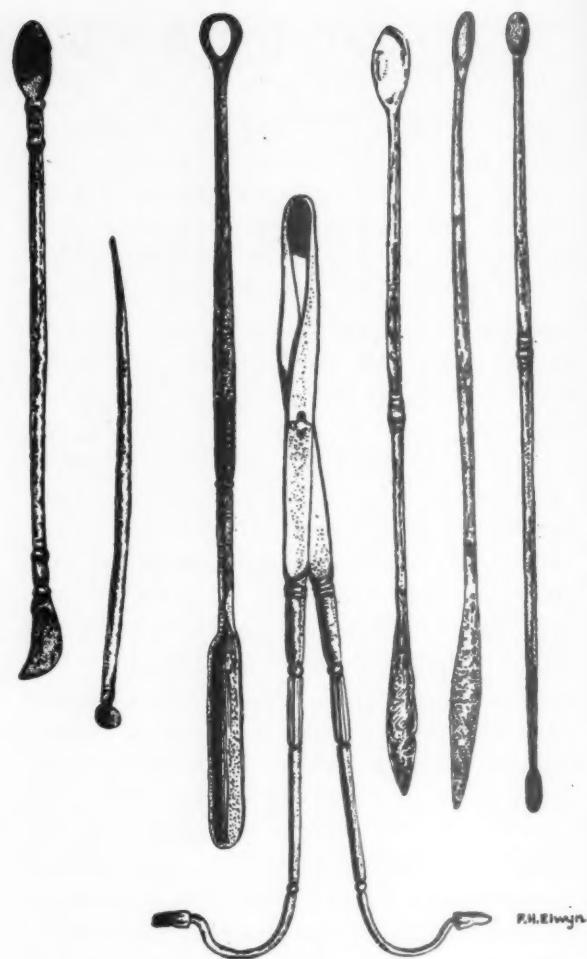


Fig. 1. Greek abortion instruments.

Results

This report is of 400 consecutive endometrial biopsies with the Randall-type cannula curette performed in the office on 371 private patients from Jan. 1, 1953, through Feb. 15, 1958 (Table I).* With the exceptions noted below, generous specimens were taken in the great majority of cases of unusual uterine bleeding or discharge. This study was not originally planned, but rather it evolved. The first stimulants were curiosity and a shortage of hospital beds, and, later, factors discussed below. The incidence of office endometrial biopsies has gradually increased until in the past year a great ma-

*Since this paper was submitted, over 200 more biopsies, revealing 5 carcinomas, have been added.

jority of problems of unusual uterine bleeding have been first investigated in the office.

The Laboratory of the Department of Obstetrics and Gynecology of Northwestern University Medical School has prepared and examined the majority of the specimens. Bouin's fixative was employed and the tissue stained with hematoxylin and eosin (Table II).

There were 5 cases with tissue insufficient for satisfactory diagnosis. The other 98.6 per cent of the specimens were adequate for histologic preparation and study. Nine of the 11 cases of endometrial carcinoma were diagnosed from the original cannula curettage. The other two showed marked hyperplasia in the biopsy and were diagnosed as cancer in the hospital after dilatation and curettage.

Eighty-three cases were followed with surgical curettage in the hospital because of further irregular bleeding, endometrial hyperplasia, and/or atypical histologic changes, with discovery of only the 2 malignancies mentioned. There were 10 endometrial polyps in the group followed by cu-

rettage, only 2 of which were suspected from biopsy material. It was of interest to find 4 small placental polyps, 11, 12, 13, and 15 weeks post partum; in 5 other cases there were old placental elements many weeks after unsuspected early spontaneous abortion. In 7 of these 9 cases, bleeding patterns returned to normal after cannula curettage. There was no apparent infection, increased bleeding, or suspicion of uterine perforation in the series. Seven patients were not traceable. None is known who failed to return because of the procedure.

Comment

An apparently widespread reluctance to perform office studies of the endometrium may stem in large measure from precedent. Randall²⁰ wrote in closing his original communication, "It should be stated that this instrument is not used for diagnosis of malignant conditions." Novak,¹⁶ however, wrote that he could remove the endometrium quite satisfactorily with a cannula curette. Mazer and Israel¹² represented the near-ultimate in office activities when they reported performing complete dilatation and curettage in the office with, at most, ethyl chloride inhalations. It may be of significance that they also noted 47.5 per cent of the patients in their series refused the procedure for at least 3 months. It is well known that dilatation of the cervix *per se* is a very painful procedure; a 4 mm. cannula curette effects a minor degree of dilatation, and a recently offered 2 mm. curette, even less.

The Papanicolaou test has tremendously enhanced the early discovery of cervical cancer, but cytologic examination of the vaginal pool is notoriously inadequate for the detection of fundal carcinoma.¹ An office procedure that can quickly clarify problems including endometrial cancer would seem to have merit beyond the prejudice of precedent and custom. In this report there admittedly are many cases that exhibited only minor variations in bleeding patterns. Yet, the patient would usually not have presented herself unless she were concerned.

Table I. General data

Endometrial biopsies	400
Patients	371
Followed by dilatation and curettage	83
Endometrial carcinoma	11
Endometrial carcinoma missed	2
Endometrial polyps present	10
Endometrial polyps missed	8
Old placental tissue	9
Pyometra	3
Tissue insufficient for diagnosis	5

Table II. Histopathologic findings

Proliferative endometrium	141
Secretory endometrium	103
"Mixed" endometrium	41
Atrophic endometrium	14
Hyperplasia of endometrium	46
Atypical endometrium	26
Carcinoma of one endometrium	9
Old placental tissue	9
Endometritis	6
Tissue insufficient for diagnosis	5
Total	400

The physician's ability to evaluate the problem is facilitated by histologic findings.

What of the patient who has abnormal bleeding after negative histologic findings? All gynecologists have found it occasionally needful in such cases to perform 2 or more hospital curettages, or even hysterectomy. These cases do not detract from the usefulness of the cannula curette. The wider use of this instrument is proposed only to reduce the number of hospital admissions for curettage; it cannot supplant a surgical dilatation and curettage in conditions not clarified by an office procedure. We agree wholeheartedly with Palmer and others¹⁹: "A single negative specimen by either method should never be considered adequate. A repeat examination by either method is imperative if the symptoms suggest the possibility of malignancy, and especially if such symptoms persist." We have preferred to do most of the "repeat examinations" by the hospital method.

There are several advantages of office biopsies:

1. There is no delay. In one survey of the delay factor in diagnosis of endometrial cancer, Howson and Montgomery⁹ found delay attributable to the attending physicians in 28.5 per cent of the 259 cases studied. The average period of physician delay was 13.7 months! In 48 per cent of this physician delay group, no pelvic examination was made! Palmer and associates¹⁹ commented on this survey, "undoubtedly some of the doctors responsible for the delay in the above cases, as well as others, would have more thoroughly investigated the presenting symptoms if such investigation did not require hospitalization and anesthesia for diagnosis. Also, undoubtedly, some patients refuse investigation because of fear of surgery and finances involved. The patient with but one episode of bleeding is especially likely to decline hospitalization for further investigation." Wall²⁸ notes that, of the private patients who were advised to have a curettage after a negative biopsy, 36 per cent did not follow through for reasons of expense, inconvenience, or procrastination.

2. Both patient and physician save a great deal of time.

3. The cost is greatly reduced. During the accumulation of this series the hospital records were sampled in cases of uncomplicated diagnostic curettages. These have revealed the office-laboratory fee to be but 10 to 15 per cent of the expense of the hospital, anesthesiologist, and surgeon.

4. Hospital beds and operating room schedules are released for more demanding operations. In these days of crowded hospitals and long waiting lists, this is of considerable advantage to the whole staff, as well as to waiting patients. Our original interest in the office procedure was stimulated by this factor.

5. Theoretically, there may be less risk of disseminating cancer cells with a cannula curette than during the pistonlike action of a solid metal cervical dilator.

Some conditions do not lend themselves to cannula curettage:

1. Endometrial polyps are missed more often than obtained. Even in doing a hospital curettage, if long, narrow "polyp forceps" are not routinely employed, polyps may be missed—to bleed again another day.

2. Many physicians feel that inadequate tissue may be obtained. Patience and gentleness usually overcome this possibility. In this series, 98.6 per cent of the biopsies provided adequate tissue for study.

3. For some patients the procedure is distressing and painful. This situation should be met, not with coercion or cajolery, but with immediate booking for a dilatation and curettage in the hospital.

4. It is felt that any instrumentation of the uterus, in cases of known or suspected complications of pregnancy, should be done in the hospital. Neither should endometrial biopsy be carried out in the presence of infection.

5. Heavy bleeding can usually best be terminated with hospital curettage. Even though cannula biopsy has preceded the resumption of normal cyclic bleeding in many patients in this study, we consider the procedure only a diagnostic one. Douglas, how-

ever, felt reversion to normal bleeding patterns was effected in an unspecified number of cases in his biopsy series.

Summary

1. Endometrial biopsy in the office is a safe, simple, timesaving, and very economical procedure in a large majority of patients.

2. Accuracy of diagnosis is high: recent literature in which patients had both biopsy and a hospital dilatation and curettage attests this in large series.

3. Endometrial polyps are frequently missed and are best removed by a hospital procedure.

4. Any lack of correlation between symptoms, physical examination, and histologic findings must be further investigated.

5. It is believed that the cannula curette may be used more extensively in the office. Such a procedure could materially reduce the number of diagnostic dilatations and curettages performed in the hospital.

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Discussion

DR. F. J. HOFMEISTER, Milwaukee, Wisconsin.
I am in agreement with the general tenure of the material presented by Dr. Burge.

I am not familiar with the report by Dr. J. H. Wall, which was published in the *American Journal of Roentgenology*. This did not appear in the original copy of the paper submitted by the essayist. I would feel that the large number of cases reported by Dr. Wall is colored by the fact that they are from a selected group and from a

clinic primarily involved with the diagnosis and treatment of malignancy.

Our own unpublished material, which will attempt a critical review of the diagnosis of gynecological malignancy in a private practice during a 9 year period, has not been completed. During this period routine Papanicolaou smears were done on all gynecological patients. Selective circumferential endometrial sampling was done during the first 5 years and routine circumferential endometrial sampling during the last 4 years.

Table I

<i>Chart No.</i>	<i>Age</i>	<i>Symptomatic</i>	<i>Papanicolaou smear</i>	<i>Endometrial biopsy</i>
4995	50	No	Negative	Adenocarcinoma
6056	62	Yes	Atypical	Adenoacanthoma
			(Papanicolaou smear 4 years earlier, negative)	
9839	47	Yes	Negative	Adenocarcinoma (in situ)
10617	80	Yes	Negative	Adenocarcinoma but failed to follow with therapy
9847	51	Yes	Negative	Adenocarcinoma
10140	78	Yes	Negative	Adenocarcinoma
6090	76	No	Negative	Adenocarcinoma (advanced)
2839	39	No	Negative	Adenocarcinoma
7720	57	Yes	Positive	Adenocarcinoma
8869	49	Yes	Negative	Adenocarcinoma
10050	73	Yes (one spot)	Negative	Adenocarcinoma
8961	42	No	Atypical	Adenocarcinoma
8199	49	Yes (spot on tissue)	Negative	Adenocarcinoma
7823	56	Yes (minimal spotting)	Negative	Adenocarcinoma
10959	56	Yes	Negative	Adenocarcinoma
9699	60	Yes (minimal spotting)	Suspicious	Adenocarcinoma (advanced)
635	40	Yes	Negative	Adenocarcinoma (in situ)
8091	56	Yes	Atypical	Adenocarcinoma
7861	70	Yes	Negative	Adenocarcinoma (advanced)
10153	83	Yes	Positive	Adenocarcinoma

The results presented are a segment of approximately 3 years, Sept. 1, 1953, to Oct. 24, 1956, during which routine circumferential sampling of the endometrium was undertaken as a part of a complete gynecological examination. Since Dr. Burge used selective sampling, endometrial evaluation on patients with symptoms, our reports are not identical.

During the stated period a total of 4,418 private patients were evaluated and, except when contraindicated by the complication of pregnancy, the absence of the uterine fundus (subtotal hysterectomy), or the presence of stenotic obstruction (in about 1 per cent), an endometrial sampling was done. Three thousand and ninety-three endometrial samplings were carried out.

Table I indicates that 20 instances of malignancy of the endometrium were found, an incidence of 0.64 per cent. In 14 of these patients the cervical Papanicolaou smears taken immediately preliminary to the sampling were negative (70 per cent); 3 Papanicolaou smears were atypical; one was suspicious; 2 were positive. It is evident that the cervical Papanicolaou smear is unreliable for the diagnosis of endometrial lesions.

If only one unsuspected malignancy had been found, the effort of thoroughness would have been justified; 4 unsuspected, asymptomatic carcinomas were found (20 per cent). An additional 20 per cent (4) of the patients had had a very minimal indication of trouble. One of the unsuspected, asymptomatic cases was far advanced. This patient is the only one that had recurrences and died.

Table II lists the additional findings in this series of cases.

During the period reviewed, and to date, when the endometrial sampling has been a part of our concept of a complete gynecological examination, there have been no known perforations or complications. Antibiotics or chemotherapeutic agents have not been used. Discomfort has been minimal.

Table II. Additional findings

Endometrial hyperplasia	158
Endometrial polyps	29
Decidua, placental or hyalinized decidual tissue	18
Endometriosis	16

The desire for completeness and thoroughness was the factor that started us in the use of the routine endometrial sampling. This was generated by the excellent results we experience with the routine Papanicolaou smear in revealing unsuspected cervical carcinomas.

The wholehearted support of Drs. E. Birge and D. Carlson, our pathologists, when they endorsed the quantity of tissue taken as adequate, encouraged us.

The primary result has been early and often unsuspected diagnosis of cancer with resultant early therapy. In average practices, the hospital bed is often more available to the patient with a definite diagnosis of cancer than to the one with suspected carcinoma. Often a scheduled, elective operation can be postponed and the bed used by the patient with a diagnosis of cancer. This expedites cancer therapy.

Although in some instances there is financial advantage with office endometrial evaluations, the so-called complete insurance coverage favors the hospitalized patient. The only goal should be early diagnosis and treatment. The quality and accuracy of the procedure must compare—and does compare—with the hospital procedure. The economy must not be the primary concern, even in this period of decreasing economy.

In no instance where a patient having a negative endometrial biopsy was operated upon was malignancy found. In 3 instances unsuspected, undiagnosed endometrial lesions were found at the time of operation. One was a prolapsed uterus which someone had previously subjected to a Watkins procedure. The cervical Papanico-

laou smear was negative. It was impossible to probe the endometrial cavity.

The second was a prolapsed uterus with a completely stenosed cervix in a menopausal woman. The cervical Papanicolaou smear was negative.

The third was a prolapsed cervical stump with a negative Papanicolaou smear which revealed a spot of blood at the os at the time of operation. Curettage revealed endometrial carcinoma in the remnants of what was called a subtotal hysterectomy. Since then, every cervical stump is gently evaluated by exploration with an endometrial curette.

In closing, I would be remiss if I did not re-emphasize the fact that I am in agreement with the essayist and feel that this procedure is extremely valuable.

Dr. R. R. GREENE, Chicago, Illinois. It has been my privilege to see and to interpret at least 100 of these endometrial biopsies for Dr. Burge. I can attest that the sampling of endometrium is very adequate.

I wonder if in some instances it isn't even more adequate sampling than that obtained from a hospital curettage specimen. The whole specimen that Dr. Burge sends us is put in the block and sections are made at three different levels. This is not necessarily the practice in hospital pathology laboratories. If the fragments are at all numerous, only some of them are blocked and then sections are cut at one level—not three. This is one reason a small carcinoma might not be discovered. The main reason a carcinoma is missed is that the curette didn't hit the right area.

Pneumopolycystic endometritis

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PNEUMOPOLYCYSTIC endometritis is a disease of the endometrium characterized by air- or gas-filled cysts up to 2 cm. in diameter; it is asymptomatic, is associated with pregnancy, and resolves without treatment. Similar cysts have been found in the cervix, vagina, vulva, gastrointestinal tract, and urinary tract.

Huguir¹⁶ first reported these cysts in the cervix and vagina of a pregnant woman in 1847. The disease has been variously termed colpohyperplasia cystica, as a Turkish maize by Winckel,³¹ vaginitis emphysematosa by Zweifel,³⁴ emphysema vaginae by Eppinger,¹⁰ pneumatosis cystoides vaginae by Nowicki,²⁷ emphysematous colpitis by Burt, Roark, and Couri,⁶ colpocervicitis emphysematosa by Mackles and Gettinger,²³ cystitis emphysematosa of the urinary bladder by Mills,²⁴ pneumatosis cystoides intestinalis (found in ileum and colon more frequently than elsewhere in the gastrointestinal tract) by Kaufmann,²⁰ and cervicocolpitis by Abell.¹ I prefer the name "pneumopolycystic" plus "-itis" of the organ involved.

While the cause of the disease is not definitely known, Baldy² said that emphysematous vaginitis is an inflammation of the vagina with gas in the small spaces and canals of the connective tissues and lymphatics at the upper end of the vagina. He said that it is usually found in pregnant women and the cysts collapse when punctured.

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In 1892, Wright³² described a case which he called emphysematous vaginitis. The disease was apparently transmitted to the patient's husband as it appeared on the glans penis a few days after coitus.

Wright³² thought that *Oidium albicans* was responsible. It is doubtful from his description that this was pneumopolycystic vaginitis since no constant symptoms have been attributed to the disease although leukorrhea and pain from pressure have occurred.

Crossen⁸ said that the disease is caused by a mild gas-forming bacillus—not *Bacillus aerogenes capsulatus*—and that the resultant gas was trimethylamine, confirming Zweifel's³⁴ view. Klauser and Welponer²¹ showed that the cysts contained oxygen and nitrogen in atmospheric concentration while Ingraham and Hall¹⁷ also found oxygen and nitrogen but added that the concentration was not pure oxygen, nitrogen, trimethylamine, or hydrogen sulfide. They suggested that the gas acted as a foreign body causing a histiocytic giant cell response of the tissues. Gardner¹² felt that the gas was endogenous in origin, while Nagashima²⁶ wrote that the cysts arise in the epithelium-forming epithelial nests in which the gas is formed by bacterial action. Buckingham and McClure⁵ stated that the pathogenesis is unknown and that the disease is asymptomatic multiple gas-filled vacuoles beneath cervical or vaginal epithelium, there is no interstitial emphysema, and each vesicle collapses audibly when punctured. Research⁵ along bacteriologic and biochemical lines has failed to isolate a causative organism or to determine the nature and composition of the gas within

the vesicles. Attempts⁵ to reproduce the disease experimentally by air injections beneath the vaginal epithelium of rabbits have failed. Eisenlohr¹¹ felt that the vaginal folds plaster together and the lining is thinned by pressure from trapped air. Oliver²⁸ suggested that carbonic acid might be formed and accumulate in the connective tissues of the vagina, and Hoffman and Grundfest¹⁵ reported about 20 per cent carbon dioxide was found in a gas analysis. Lindenthal²² isolated a bacillus on an anaerobic growth medium which produced hemorrhagic edema with gas formation when injected into subcutaneous tissues of guinea pigs and mice. Findings pertaining to emphysematous *Bacillus vaginalis* have not been substantiated by later investigators. Kaufmann²⁰ and Jackson and Wright¹⁹ both felt that the lymph vessels were the site of gas formation. Montanari²⁵ wrote that the gas accumulates in the tissues evoking foreign body giant cell response; cysts form and are resolved by bursting following growth and development in the tissues. Chiari⁷ first described the foreign body giant cells of this disease in 1885 but they are not unique for this pathologic entity since Buchmann⁴ described similar giant cells in colpitis lipomatosa. According to Zachariae³³ round cell infiltration, eosinophils, and giant cells may be present but there is lack of complete agreement as to whether the lining is fibrous tissue, endothelial cells, or other elements, or if giant cells must be present.

The vast majority of reported cases of pneumopolycystic disease have been associated with pregnancy although this is not a requisite of the entity. It is a rare disease as less than 100 cases have been reported. Bender and Jeffcoate² reported 2 cases in 1950. One was associated with an abortion in the eighteenth week; the other was diagnosed at 26 weeks gestation and disappeared at 32 weeks gestation and the patient went on to term and was delivered of a normal baby. Schmolling³⁰ reported one case in the fifth month of pregnancy. Mackles and Gettinger²³ reported a case associated with abortion at 2 months gestation. Darling⁹ reported the case of a woman who had the disease in

2 consecutive pregnancies and that of another woman who had dyspareunia with the disease although this could have been due to other pelvic conditions. Robberson and Owen²⁹ reported on a patient who had the disease twice in consecutive pregnancies in the period of 2 years.

Ingraham and Hall^{17, 18} discussed Gardner's¹² case in which the patient complained of being conscious of the bursting of the cysts. Although Gardner's patient had cysts located on the vulva, most reported cases have involved the cervix and upper two thirds of the vagina. Burt, Roark, and Couris⁶ stated that the disease can be limited to one side only, and Eisenlohr¹¹ described a woman with pneumatosis cystoides intestinalis and pneumopolycystic cervicitis coexistent. Buckingham and McClure⁵ reported 2 cases emphasizing that it may be difficult to distinguish the disease from cervical carcinoma and that multiple biopsies may be needed to differentiate the two lesions. Hoffman and Grundfest¹⁵ reported the case of a woman

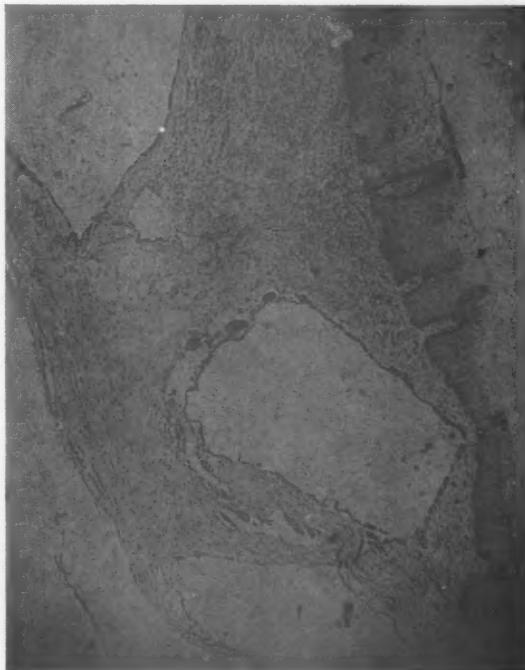


Fig. 1. Low-power view of sections of cervix (Case A43959), showing multicystic character of the lesion and cysts varying in size.

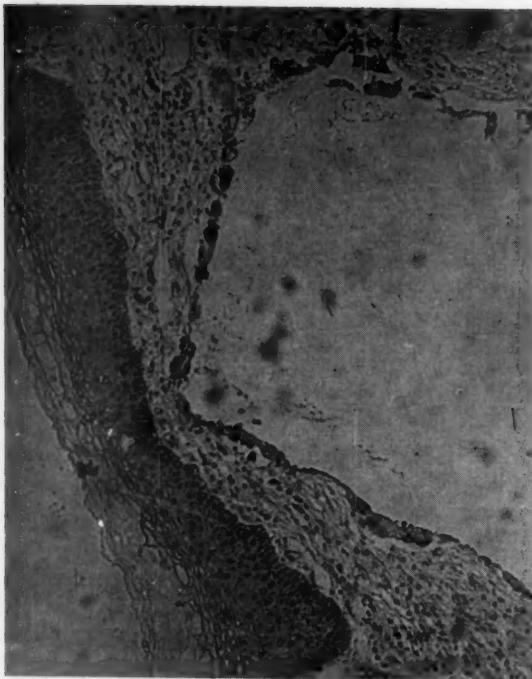


Fig. 2. Higher power, same field, showing intact surface squamous epithelium with underlying cyst lined by multinuclear giant cells and endothelial cells. Stroma shows scanty infiltration by leukocytes.

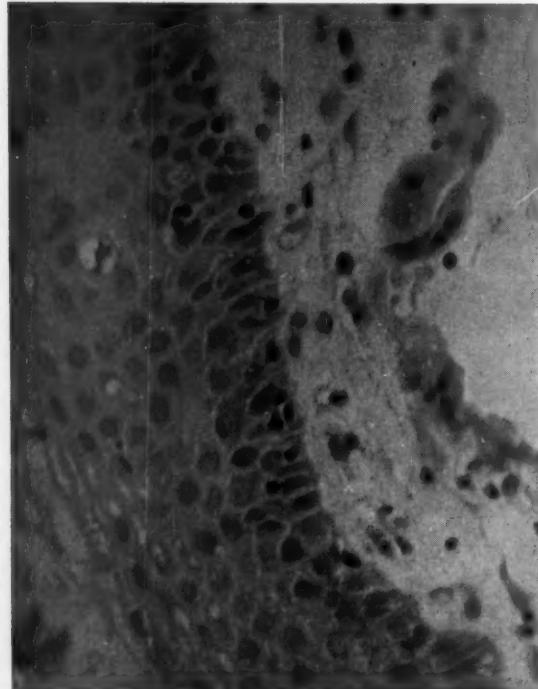


Fig. 3. High power, same field, showing detail of multinuclear giant cells lining cyst wall.

whose presenting complaint was contact bleeding which biopsy revealed was caused by pneumopolycystic cervicitis.

Pneumopolycystic cervicitis has appeared between age 17 years¹⁰ and 76 years.²⁷ While it usually disappears from a few days to 2 weeks after delivery, it has lasted for 4 months according to Robberson and Owen.²⁹

Zachariae³³ reports 10 cases—2 his own—in nonpregnant women. In addition, Buckingham and McClure⁵ reported one case in a patient who had had a supracervical hysterectomy 13 years prior to occurrence of vaginitis emphysematosus which follow-up examination revealed to be cleared up after 2 weeks on tetracycline vaginal suppositories. They reported another case in a 37-year-old woman who died of endocarditis with pneumopolycystic vaginitis as an incidental autopsy finding. Heaney¹³ reported a case 2 years after subtotal hysterectomy in a 40-year-old unmarried woman which cleared up without treatment 3 weeks after cervical biopsy showed the typical microscopic picture of pneumopolycystic cervicitis. Herman¹⁴ reported one case of pneumopolycystic vaginitis in a 28-year-old nullipara. Abell¹ recently reported 8 cases not associated with pregnancy. Four were incidental autopsy findings and 4 were diagnosed by biopsies taken to rule out carcinoma of cervix and vagina, the primary complaint being leukorrhea. Six of his cases were in patients who had passive congestion with hypoxia which he suggests may predispose to the development of the cysts which he feels may be more common than reports would indicate.

Case reports

Case 1. (A43959) A 32-year-old Mexican gravida ii, para i, whose first pregnancy was uncomplicated and whose estimated date of confinement was July 21, 1959, was admitted to the hospital on July 12, 1959, in active labor. Five hours later a normal male infant was delivered spontaneously from the left occipitoanterior position. A 4 by 3 by 2 cm. sessile, cystic cervical polyp was excised and innumerable additional cysts 1 to 2 mm. on up to 2 cm. in diameter, which popped when compressed, were seen



Fig. 4. Anteroposterior view showing pneumopolycystic endometritis.



Fig. 5. Lateral view showing pneumopolycystic endometritis.

throughout the vagina down to the vulva and involving the entire cervix and endocervix. No fluid was found in the cysts but an odorless gas was noted. The uterus was explored and found to contain cysts of similar characteristics throughout the endometrium.

The cervical polyp floated in preserving solution. This and vaginal biopsies showed numerous cystic spaces of variable size and contour lying in an edematous connective tissue stroma underlying an intact covering of well-differentiated stratified squamous epithelium (Fig. 1). Most of the cystic spaces appeared to be completely empty but a few contained a small amount of eosinophilic colloid-like material. The larger spaces were lined in places by flattened cells of endothelial type. Others appeared to be lined by attenuated or flattened multinuclear giant cells (Figs. 2 and 3). Occasional giant cells were also present in the stroma adjacent to the cyst walls. In a few of the cysts no definite lining cells were noted, the inner surfaces appearing to be comprised merely of the edematous connective tissue stroma. The latter showed evidence of moderate to marked vascular congestion with abundant dilated blood-filled vascular spaces. In addition, there was evidence of mild subacute and chronic nonspecific inflammation with foci

of infiltration by neutrophils, rare eosinophils, lymphocytes, and plasma cells. The inflammatory reaction in general was diffuse, showing no particular relationship to the cystic structures.

X-ray films of the pelvis taken on the second postpartum day showed innumerable gas-containing cystic structures outlining the entire uterus and varying in size from 1 to 20 mm. Many appeared confluent. A membranous line of increased density was present in the region of the endometrium, which was surrounded by the cysts. The size of the uterus was consistent with incomplete involution. No concretions were noted. The bony structures are not remarkable (Figs. 4 and 5).

Case 2. (H55325) A 25-year-old white gravida ii, para i, whose first pregnancy was uncomplicated, was seen in the ninth week of her second pregnancy and "cystic cervicitis" was noted. No further complications occurred and she was admitted to the hospital at term in labor. Low forceps delivery of a normal child took place 8 hours later. Examination of the cervix showed it to be immensely hypertrophic and cystic, particularly the anterior lip, almost resembling a hydatidiform mole. Thousands of vesicles were present, ranging in size from 2 mm. to 2 cm. in diameter. When punctured,

they collapsed with a popping sound. They contained gas but no fluid. Cervical biopsy specimens were obtained and were found to be identical histologically to those in the first case except that more multinuclear giant cells were seen lining the cystic spaces.

Both of these cases cleared spontaneously about 2 weeks post partum.

Summary

The first diagnosed case of gas-filled cysts in the endometrium is presented. A new

name, "pneumopolycystic endometritis," is suggested for this disease.

A case of pneumopolycystic cervicitis is also reported.

A brief review of the literature dealing with gas-filled cysts is presented. These cases have been selected to point out the clinical characteristics of the pneumopolycystic disease.

Thanks are due Drs. G. W. Hewitt and P. Rivera for permission to review these cases in detail, and to Dr. Florence Rhudy, for the pathologic description.

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Effect of a radiation opaque, water-soluble medium on the histopathology of the endometrium

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A HYSTEROSALPINGOGRAM and cervicogram can be of value in the investigation of primary and secondary infertility. However, in an effort to eliminate any unnecessary irradiation of the patient,³ its use should be limited. Those patients with primary infertility who have evidence of tubal occlusion, either on pelvic examination or by a previous Rubin test, especially when tubal plastic procedures may be contemplated, warrant an x-ray examination, as do patients with infertility secondary to repeated abortions since the hysterosalpingogram is the most satisfactory method of diagnosing an anatomical uterine defect.

During the past 8 years it has been our practice occasionally to perform a curettage at the time of a hysterosalpingogram, or shortly thereafter, on patients who are having investigations for infertility or repeated miscarriages. The purpose of the present investigation is to determine (1) if this practice might be in any way harmful to the patient and (2) if the interpretation of the endometrial findings is histologically valid. There is an extensive literature on the subject of tissue damage following radiologic procedures.^{1, 2, 4-9}

During the years 1950 to 1955, some 335 patients were subjected to hysterosalpingog-

raphy with use of a water-soluble medium,* and there were 120 of these patients whose curettings were available for examination. Twenty-three patients were curetted immediately following the hysterosalpingography, 28 patients were curetted within the month and 22 were curetted in a cycle later than the following month. Forty-seven patients were curetted prior to the hysterosalpingography and serve as a control series. Specimens have been examined by one of us without knowledge of the relationship of the x-ray procedure to the curettage. The endometrium was evaluated according to the cycle and with special reference to any inflammatory change or other tissue reaction.

Pathology

The vagaries of the histologic patterns in the endometrium are well known to any who has attempted to evaluate the over-all glandular pattern, stromal edema, and cellular infiltrate. Cyclic changes produce variations in all of the features and only empiric criteria can be established to differentiate the physiologic from the pathologic. The common glandular changes during the cycle have been well documented and are briefly centered around increased coiling

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and tortuosity of the gland, mitotic activity of the epithelial cells, increase in height of the cell during the estrogenic phase, and the secretory activity during the progestational phase of the cycle. Variations in the glandular situation of a benign nature include (1) areas of "immature" epithelium, especially noted in polyps, (2) metaplasia, as noted also in polyps, and chronic inflammatory or irritative conditions, and (3) the presence of inflammatory exudates in the lumina. Stromal cyclic changes are more complicated and include (1) mitotic activity during the proliferative phase, (2) edema of the functioning layers, usually beginning at midcycle and progressing through the secretory stage, (3) coiling of the spiral arterioles with eventual breakdown of the walls through anoxemia, (4) terminal increase in size of the stromal cell in the compact layer due to additional cytoplasm, and (5) diffuse infiltration of the stroma with white blood cells and formation of lakes of blood in the stroma. The diagnosis of endometritis is a difficult one due to these latter changes, and the problem is increased when it is recognized that the basal layer of the endometrium often contains scattered foci of round cells and occasionally a sparse sprinkling of these cells throughout the stroma.

In view of the above facts, a diagnosis of endometrial infection is made only in the presence of diffuse infiltration of the stroma during phases of the cycle when such is not characteristically seen, exudates in the glands other than at the time of breakdown during menses, abnormal edema in the proliferative phase, or chronic changes such as metaplasia.

The sections in all of the cases of the study had been previously diagnosed as to phase in the cycle and abnormality if one existed. Each was subsequently reviewed without knowledge as to whether radiopaque material had been introduced before or after the curettage. Results are tabulated below.

1. Of the 47 patients who were curetted prior to hysterosalpingography, 4 showed

evidence of some endometrial reaction. One was felt to have infection in a polyp, since the endometrium associated with the reaction was proliferative while the remainder was premenstrual. Another showed a diffuse reaction with evidence of chronicity in the form of metaplasia. The endometrium was secretory in the other 2 cases but not felt to be late enough to justify the diffuse, general infiltration and individual foci of round cells. These latter two criteria would justify the diagnosis of endometritis.

2. Of the 23 patients curetted immediately after radiography, 3 showed endometrial infiltration. In 2 polyps were felt to be present. This fact was based largely on the hyperplasia present in isolated fragments with chronic inflammation in one of the 2. The final section was diagnosed as late secretory endometrium, and the infiltration was probably within normal limits.

3. Of the 28 cases curetted within the month after injection of the radiopaque material, there were 2 instances of endometrial reaction. One of these was quite diffuse but extremely mild with scattered plasma and a few polymorphonuclear cells; this appeared 24 hours after the injection. The second patient was curetted 10 days after hysteroscopy, and rather diffuse reaction without luminal involvement was demonstrated.

4. Of the 22 patients curetted more than 30 days after radiography there were no instances of inflammatory change suggesting that the endometrium recovered satisfactorily from whatever mild reaction the radiopaque fluid might have produced initially.

Clinical data

There were only 3 patients in the entire group who had any untoward clinical symptoms. One had lower abdominal pain with no abnormal pelvic findings. This patient had had a successful Rubin test and an unsuccessful hysteroscopy. Two patients had fever; one reaction was reported by the patient and not confirmed by the physician and occurred following a hysteroscopy for repeated miscarriages; the other followed an

x-ray examination which demonstrated patent tubes and myomata uteri. Neither patient developed any pelvic masses and the endometrium obtained 2 and 7 days after hysterosalpingography showed no evidence of inflammation in either case.

The 71 patients who had hysterosalpingography prior to the curettage have been evaluated according to the reason for the procedure, the x-ray findings, and the correlation with the Rubin test as well as the occurrence of pregnancy following the procedure.

Fifty examinations were done for the investigation of infertility and 20 for the investigation of repeated miscarriages; one was to confirm the diagnosis of traumatic amenorrhea (Asherman's disease). Forty-five of the patients had also been investigated with Rubin tests.

Twenty-five patients had successful Rubin tests and successful hysterosalpingograms in that tubal spill was demonstrated on at least one side. Five of these patients, however, showed some evidence of tubal pathology; unilateral tubal occlusion was demonstrated by x-ray examination four times, and one patient had a Rubin test which was successful only at high pressures. Although there were 11 pregnancies in this group only 2 were judged as probably related to the performance of the hysterosalpingogram in that these 2 patients had had previous evidence of tubal occlusions. One of these pregnancies terminated in an ectopic pregnancy; this was the patient who had a Rubin test that was successful only at pressures of over 200 mm. of mercury.

There were 8 patients in whom tubal patency was not demonstrated radiologically although the Rubin tests had been successful. There were no pregnancies in this group. Although there was no instance of an unsuccessful Rubin test with a hysterosalpingogram which showed bilateral spill, this has also occurred in our experience. When conflicting results are obtained in tubal patency tests, we are inclined to agree with Rubin that there is some technical difficulty and the tests should be checked until one is sure

on which side the error has occurred. A successful hysterosalpingogram, however, is, of course, unequivocal evidence that the tubes are patent unless the interpretation of the x-ray film is incorrect, which may occur when a hydrosalpinx is present.

Tubal occlusion from pelvic inflammatory disease was demonstrated radiologically and by the Rubin test in 12 patients. There were no pregnancies in this group. The occurrence of tubal occlusion in 20 of 45 cases indicates a high rate of potentially infected patients in the series, and the fact that only 3 minor reactions occurred in 120 procedures has been most gratifying. It has been our practice to maintain our clinic patients on a broad-spectrum antibiotic 4 days prior to and 3 days following a Rubin test. Perhaps this may have contributed to the good results.

Twenty-six patients had hysterosalpingography only without associated Rubin tests. There were 11 pregnancies in this group. However, 9 patients had been investigated for repeated miscarriages and only 2 who became pregnant had been subjected to the procedure because of infertility. One of these two pregnancies, it seems, can perhaps be attributed to the procedure as there was no other demonstrable factor and the patient became pregnant immediately thereafter. The second patient, however, had an ectopic pregnancy, and the hysterosalpingogram had been done to demonstrate tubal patency following a salpingectomy for a previous ectopic pregnancy. The second ectopic pregnancy occurred about a year after the procedure and, it is thought, had nothing to do with the hysterosalpingogram.

Of the 20 patients investigated for repeated miscarriages, 9 in the group were found to have some form of congenital septate uterus and 3 had myomata uteri.

Conclusion

There were some 50 hysterosalpingograms performed for infertility, 23 of which showed tubal occlusion from pelvic inflammatory disease. A water-soluble radiopaque medium was used. Of the whole group, after

analysis of infertility according to factors, it was thought that perhaps 3 pregnancies were attributable to the hysterosalpingograms. One of these 3 pregnancies terminated in an ectopic pregnancy. There was no evidence, either clinically or pathologically, of a tendency for exacerbation of an old pelvic inflammatory disease following the procedure, and only 3 patients had mild clinical symptoms of a nonspecific reaction characterized, in one case, by abdominal pain and in 2 instances by a low-grade fever of 2 days duration.

There were 20 examinations made to determine the cause of repeated miscarriages. An unexpectedly high rate of uterine anomalies occurred in this series. Nine con-

genitally defective uteri and 3 submucous fibroids were demonstrated. One examination was made to confirm the diagnosis of traumatic amenorrhea.

In the group of patients who had had a hysterosalpingogram prior to the curettage the histologic findings were indistinguishable from those in patients who had had hysterosalpingography following the curettage. It would seem that the use of radiation opaque, water-soluble medium is seldom associated with endometrial reactions, that it is safe to proceed with an immediate curettage clinically, and that the interpretation of the histologic findings, following the procedure, is valid.

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The delay period in carcinoma of the vagina

With observations on age incidence and survival rate

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CARCINOMA of the vagina is one of the rare types of female genital tract carcinoma, being only slightly more frequent than carcinoma of the Fallopian tube. The cause is unknown. The main symptom is bleeding, and an ulcerative lesion is usually seen on examination. When located near the cervix the spread resembles cervical malignancy; when near the vulva the spread follows that of vulvar carcinoma. Definitive diagnosis is made by biopsy. Because of the lack of large series of cases, there is no widely accepted standard method of management, and prognosis is usually considered to be poor.

Material and methods

The material to be presented was taken from the files of the Philadelphia Committee for the Study of Pelvic Cancer, an organization founded in 1945 by the Obstetrical Society of Philadelphia with the cooperation of the Philadelphia County Medical Society and the financial aid of the Philadelphia Division of the American Cancer Society.^{1, 2} The prime purpose of the organization has been the evaluation of the delay period in the diagnosis of gynecologic cancer.

Patterned on the model of a maternal mortality committee, monthly luncheon meet-

ings are held at which time case histories, previously investigated by trained workers, are reviewed. Physicians associated with the case are invited to participate in the discussion.

All case records from the committee were reviewed first by two gynecologists (W. R. L. and L. J. G.) and then re-reviewed with a statistician (H. M.). Only cases of undoubtedly primary vaginal malignancy were included. Follow-up was 100 per cent to January, 1959.

Results

For comparative purposes, the relative frequencies of the various types of gynecologic malignancy studied by the committee were determined (Table I). Until Jan. 1, 1959, a total of 5,399 cases of carcinoma of the female genital tract had been investigated. The cervix was primarily involved in almost two thirds of the cases; carcinoma of the vagina occurred in only 1.4 per cent. The ratio of the frequency of cervical to vaginal carcinoma was 43 to 1.

Our patient material is outlined in Table II. A total of 76 patients was studied. The youngest patient was 21, the oldest 87. We were able to determine parity in 69 of the 76 women; of these, 74 per cent were parous. Seventy-four per cent were white; 26 per cent were Negro. This agrees approximately with the percentage of Negroes in the Philadelphia population and therefore shows no evidence of racial selectivity. Three

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Table I. Relative frequency of female genital cancer

Site	No.	%
Cervix	3,252	60.2
Corpus	1,241	23.0
Ovary	602	11.1
Vulva	208	3.9
Vagina	76	1.4
Tube	20	0.4
Total	5,399	100.0

Table II. Patient material (76 cases)

Age at diagnosis	Youngest 21; oldest 87; mean 55
Race	White 56 (74%); non-white 20 (26%)
Status	Ward 57 (75%); private 19 (25%)
Parity	Nonparous 18 (26%); parous 51 (74%); (unknown 7)
Histology	Squamous 68 (89%)
Hospitals	33

fourths of the patients were ward and one fourth were semiprivate or private patients. Patients from 33 different hospitals were evaluated.

Data on the age distribution of our patients are presented in Table III. The first column is a listing of decades; the second column indicates the age distribution of the subjects studied. From this latter column it is seen that the frequency rises only slightly from the 40's to the 50's, is the same for the 60's as the 50's, and then declines at the older ages. This, however, may

not be taken as any indication of the age incidence of vaginal carcinoma since, in the third column, the frequency with which women in the various age groups are found in the general Philadelphia population³ shows a decline after age 40. While it is not possible to compute any precise values for age incidence, differences in the ratio of patient to population percentage (column 2 divided by column 3) reflect differences in the age incidence of vaginal carcinoma (column 4). In the last column the ratio of the decade 20 to 29 has arbitrarily been designated as 100 and subsequent ratios related to this figure. It is seen, therefore, that incidence is a function of increasing age and that incidence of carcinoma of the vagina is approximately 8 times as high among those over 70 years of age as among women in their 20's.

Histologic diagnoses are tabulated in Table IV. The vast majority showed squamous cell carcinoma (89 per cent). There were, in addition, 4 cases of adenocarcinoma and one each of undifferentiated carcinoma, malignant melanoma, sarcoma, and hemangiopericytoma.

The initial symptoms of the patients are outlined in Table V. Bleeding alone occurred in almost half of the patients. Bleeding was combined with vaginal discharge and/or urinary complaints in another one fourth of the patients. Discharge or urinary complaints were the only symptoms in 15 per cent.

A qualitative analysis of delay (Table

Table III. Age distribution in relation to general population

Age at diagnosis	Distribution		Ratio of patients to population	Incidence index
	76 patients (%)	Philadelphia female population, 1950 (%)		
20-29	8	23	0.35	100
30-39	11	23	0.48	140
40-49	17	20	0.85	240
50-59	22	16	1.38	390
60-69	22	11	2.00	570
70-79	15	7	2.86	820
80-89	5			
Total	100	100		

VI) showed that there was no delay of any type in one fourth of patients. In somewhat less than half of the cases the patients were responsible for delay and, in almost an equal percentage, physicians (including institutions) were responsible for delay. It is interesting that the patients themselves were the sole source of delay in about one third of the cases and physicians were the sole source of delay in approximately the same proportion. The term "delay" as used here means an elapsed time of more than one month from onset of symptom(s) to consulting a physician (patient delay) or an elapsed time of more than one month from the patient's first visit to diagnosis (physician delay).

Duration of delay was analyzed quantitatively by source; i.e., patient, physician, or institutional. It is our feeling that institutional delay was almost invariably caused by the physician and the two sources were combined (Table VII). The first column indicates time interval of delay in months. Subsequent columns indicate different types of delay. The length of physician delay was approximately the same as the length of patient delay. For example, in 13 per cent of cases patient delay was over 8 months; in 15 per cent, physician delay was more than 8 months. Unfortunately, delays from various sources were frequently additive so that in more than one fourth of cases there was a total delay to diagnosis of 8 months or more. In over one half of cases there was a total delay in excess of 4 months. Delay from diagnosis to treatment was infrequent (Table VIII). In 90 per cent of cases there was no delay whatever.

As a matter of interest, the various types of therapy were determined (Table IX). Treatment varied from none through what seemed to be definitive radical operations. No relationship was observed between type of treatment and survival since, even with immediate therapy, survival ranged from a few months to many years. It must be admitted, however, that the exact extent of the lesion when diagnosed could not be ascertained from the records available.

Table IV. Histologic diagnoses

<i>Cell type</i>	<i>No. of patients</i>	<i>%</i>
Squamous cell	68	89
Adenocarcinoma	4	
Undifferentiated	1	
Sarcoma	1	
Malignant melanoma	1	
Hemangioendothelioma	1	
Total	76	100

Table V. Initial symptom(s)

<i>Symptom</i>	<i>No. of patients</i>	<i>%</i>
Bleeding only	36	47
Bleeding plus		
Discharge	9	
Urinary	2	
Other	6	
Total	17	24
Discharge or urinary	12	15
Others (exclusive of above)	11	14
Total patients	76	100

Table VI. Delay between initial symptom(s) and diagnosis

<i>Source of delay</i>	<i>No. of patients</i>	<i>%</i>
No delay	18	24
Patient only	26	34
Patient plus physician (including institution)	35	46
Physician only	9	12
Total	32	42
Total patients	76	100

When survival rates were calculated (Table X), it was observed that 14 per cent of all patients had survived 5 years or more and half of these were still alive and well 5 years after treatment. An additional 13 per cent may still attain a 5 year survival since they are at present alive and presumably well. Thus, the 5 year survival rate is at least 14 per cent for this series and may reach 27 per cent. It should be noted that 68 per cent died either of or with cancer within 5 years after treatment.

An attempt was made to seek relationships between delay period and survival

Table VII. Delay between initial symptom(s) and diagnosis

Time interval (months)	Source of delay (%)				
	Patient	Physician	Institution	Total physician (including institutional)	All sources
1 or less	54	63	93	58	22
2-3	24	14	4	13	25
4-7	9	11	1	14	24
8-15	9	7	1	8	16
16-31	3	1	1	3	8
32-63	0	4	0	4	4
64 and over	1	0	0	0	1
Total patients	100	100	100	100	100

(Table XI). Three years was chosen as the dividing line since there were so few patients who survived over 5 years. For all patients, the median delay was 4 months. Unfortunately, we are unable to say that those patients with the least delay had the longest survival since no such relationship is apparent from the data. The 58 patients who died within 3 years, either with or of cancer, had delays from 0 to 58 months while the 10 patients who were still alive and well after 3 years had delays of approximately the same duration. It was not possible, from the data available, to ascertain the reasons for this, although possible hypotheses can be advanced.

Table VIII. Delay (diagnosis to treatment)

Source of delay	No. of patients	%
No delay	69	90
Patient	5	7
Patient and physician	0	0
Physician	2	3
Total patients	76	100

Table IX. Treatment

Treatment	No. of patients	%
None	6	8
Radium	8	11
X-ray	20	26
X-ray and radium	14	18
Definitive operation	16	21
Palliative operation	2	3
Combinations	10	13
Total	76	100

Table X. Survival of patients

Survival status	No. of patients	%
Survived 5 years plus	11	14
Died with cancer	4	5
Died without cancer	1	1
Living without cancer	6	8
Still alive, no cancer		
Under 5 years	10	13
Died under 5 years	55	73
Without cancer	4	5
With cancer	51	68
Total	76	100

Comment

Our relative frequency of vaginal carcinoma (1.4 per cent), compared with all types of female genital tract carcinoma, agrees with the frequency recorded by others.⁴⁻⁸ Cervical carcinoma in our series was 43 times as frequent as vaginal carcinoma; Douglas reports a ratio of from 35 to 45 to 1.

In reports by others,^{4-6, 8} the average age of women with vaginal carcinoma is usually stated to be in the early to middle 50's. The corresponding value for our group was age 55. Even more interesting than the average age, however, is the wide range of ages encountered; the youngest of our patients was 21 while the oldest was 87 at the time of diagnosis. Our conclusion that there is a direct relationship between incidence of vaginal carcinoma and age is in substantial agreement with the findings of Kaiser. The difference is that Kaiser reported that the

Table XI. Delay period versus survival

Last known status	Length of follow-up	
	Under 3 years	3 years and over
Living		
With cancer		
Without cancer	6 patients; average delay: 3.5 months (range: 0-8 months)	10 patients; average delay: 6 months (range: 2-56 months)
Dead		
With cancer	58 patients; average delay: 3.5 months (range: 0-58 months)	7 patients; average delay: 5 months (range: 0-86 months)
Without cancer	3 patients (range: 7-24 months)	2 patients (range: 2-11 months)

incidence stabilized after age 60 while our incidence index continued to rise. Discrepancies between the two studies are probably due to the rather small number of subjects available for study.

Bleeding was the most frequently reported initial symptom (71 per cent). This agrees roughly with the literature: Way (68 per cent), Brack and associates (71 per cent), Livingston (76.4 per cent), and Merrill and Bender (82 per cent).

While the rather high incidence of patient delay is not condoned, it is understandable. The high incidence of physician delay is, however, quite inexcusable. From interviews with the patient, it is apparent that in most cases the failure to reach a prompt diagnosis cannot be explained on the basis of early stage of disease with minimal or imperceptible lesions. Rather, the major factor was failure on the part of the physician to examine the patient at all, or undue delay before an examination. The reasons for patient and physician delay have been adequately summarized elsewhere¹³ and need not be reviewed here.

Our failure to find any relationship between prognosis and either type of treatment or length of delay period should not be taken as evidence that no such relationships exist. It would seem incredible, for example, to argue that in a given patient it makes no difference whether treatment is started immediately or is delayed for a year. Rather, the lack of correlation is doubtless due to the wide variety of unknown variables such as differences in extent of disease

at time of diagnosis, differences in rapidity of growth of the malignancy, difference in time in the course of the disease at which symptoms appear, and other factors.

Summary

From our data we have concluded that:

1. The incidence of carcinoma of the vagina is related to increasing age.
2. No racial predisposition was noted.
3. The most common presenting symptom was abnormal vaginal bleeding.
4. In approximately 25 per cent of cases there was no delay in diagnosis. The incidence of physician delay was about the same as patient delay. In approximately 30 per cent of cases, the total delay to diagnosis exceeded 8 months.
5. There was usually no delay from diagnosis to treatment.
6. Fourteen per cent of the patients have already survived more than 5 years.
7. No relationship could be observed between length of delay and outcome.

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Carcinoma of a diverticulum of the female urethra

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THE close association of the urinary and reproductive organs in early formative stages as well as in adult life requires the gynecologist to pay as much attention to the urinary tract as to the genital tract.¹ A diverticulum of the female urethra would be an interesting example of a genitourinary syndrome diagnosed and treated by gynecologists as well as urologists.

Single or small groups of urethral diverticula² have been reported from time to time since the first report in 1805. Until recently most of these reports have dealt with diverticula which were large enough to be palpated vaginally, and the condition was considered rare. With improved diagnostic methods, such as panendoscopy and urethroradiography, however, smaller ones have been discovered with increasing frequency.

At Johns Hopkins Hospital from 1890 to 1949, only 30 cases were diagnosed and treated. In the succeeding 5 year period, after a review of the previous cases,³ 41 additional cases were diagnosed.

There is considerable difference of opinion among investigators as to the origin of diverticula of the urethra. In general, the theories embrace a congenital origin or an acquired

disease process. The latter theory is favored by American investigators.

It is probable that some diverticula originate in pre-existing normal glands or ducts that have become pathologically altered or stenosed. Also, it is possible that some others originate in normal epithelial crypts or folds that have become adherent or occluded by trauma or infection.

Some paraurethral ducts and glands, with or without cystic enlargement, may remain asymptomatic for years until some secondary pathological change or trauma supervenes.

Symptoms

The most frequent symptoms of urethral diverticula are those suggesting chronic recurring cystitis, namely, frequency urgency, and dysuria. Dyspareunia and localized pain are often complained of by patients with larger sacs. Occasionally, they complain of a bearing down sensation or have difficulty starting the flow of urine.

In carcinoma of the urethra the early symptoms are similar.⁴ Burning and itching of the meatus, incontinence, urinary retention, tenesmus, and bloody or serous discharge are present in the more advanced cases. After the lesion becomes ulcerated, it becomes tender to pressure and to contact with urine. In some patients with diverticulum or carcinoma there are no urinary symptoms, or they are so mild they are overlooked by the patient, and the pathological condition is discovered during an examination for something unrelated.

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Signs

In patients with large diverticula, a fluctuant mass can frequently be palpated vaginally, and pressure on the sac will result in an escape of purulent urine or pus from the meatus. When carcinoma is present, pressure on the sac often results in extrusion of tumor tissue into the urethra. The smaller, nonpalpable ones can be diagnosed only by observation of the orifice through a panendoscope or by urethrography.

Treatment

An uninfected or quiescent urethral diverticulum may be removed surgically from the vaginal side and the urethra closed in

layers over a catheter or sound. Some diverticula are so infected that they are really abscesses and can be treated only by incision and drainage.

There are four general types of treatment utilized for carcinoma of the urethra. Radical excision of the urethra including a portion of the vesical neck or a less radical excision leaving the vesical neck and sphincter intact are the two surgical approaches. The radiological advocate uses knife or electro-surgical excision followed by irradiation or irradiation alone.

The results of the treatment of urethral carcinoma, in general, have been very poor. Some of the best results were obtained by

Table I. Summary of known cases of carcinoma of a diverticulum of the female urethra*

Reviewer	Age (years)	Symptoms	Clinical diagnosis	Primary treatment	Later treatment	Survival	Pathological diagnosis
Wishard and Nourse	39	Burning, nocturia, frequency, difficulty in voiding, and bleeding	Palpable mass; bloody discharge	Diverticulectomy		Living and well at present (7 years)	Transitional cell carcinoma
Hamilton and Leach	53	Stress incontinence, vaginal bleeding, and vaginal discharge	Palpable mass	X-ray; diverticulectomy	880 mg. hr. radium to local recurrence 11 months later	Died of secondary carcinoma (liver and lungs) (19 months)	Adeno-carcinoma
Roth	40	Bleeding from urethra during and between urinations	Palpable mass; extension of tissue from urethra	Total urethrectomy; partial vaginectomy cystostomy		Living and well with permanent cystostomy (4 years)	Transitional cell carcinoma
Brown	40	Recurrent burning, frequency, and nocturia	Palpable mass; purulent discharge	Diverticulectomy	Excision of scar and radon seeds	Living and well (3 years)	Adeno-carcinoma
Sigmund	44	Frequency, dysuria, and difficulty in voiding	Palpable mass	Diverticulectomy	Radium needles and cystotomy; chordotomy	Living (3½ years); local extension	Epidermoid carcinoma grade III
Melnick and Birdsall	50	Occasional nocturia, vaginal discharge	Palpable mass; bloody discharge	Radium needles, 8,000 r	Radium needles, 8,200 r 30 months later	Living and well (33 months)	Transitional cell carcinoma

*All patients were nulliparous with the exception of Roth's patient, in whom parity was unknown.

Fagan and Hertig,⁴ who reported a 50 per cent 10 year cure rate in a series of 8 cases treated mainly by irradiation. Brack and Dickson⁵ reported that 54 per cent of their patients treated over 5 years previously were well. Four of them were treated with irradiation alone, and 2 had additional operations in the belief that the carcinoma had not been cured by the radiation therapy. However, no viable cancer cells were found in the surgical specimens.

In carcinoma in a urethral diverticulum there are so few cases that there is no standard treatment. This will be amplified in the following discussion.

Review of the literature

Carcinoma of the female urethra comprises only 0.02 per cent of all gynecological malignancies. The ratio of urethral diverticula to other gynecological admissions is about 1:2,300. The simultaneous coexistence of a carcinoma in a diverticulum would therefore be even rarer.

In 1951, at a meeting of the American Association of Genito-Urinary Surgeons, Dr. William N. Wishard,⁶ of Indianapolis, reported the first case of a patient with transitional cell carcinoma of a urethral diverticulum.

At about the same time, however, Hamilton and Leach⁷ reported an adenocarcinoma arising in a urethral diverticulum. Roth,⁸ in 1953, reported 3 cases of carcinoma of the urethra and included one in a diverticulum. A fourth case was reported by Brown in 1956.⁹ A fifth case, previously unreported, is that of a patient of Dr. William Sigmund of Columbus, Indiana. This case presentation would then be the sixth report of this rare and unusual subject (Table I).

Dr. Sigmund¹⁰ has kindly permitted us to report on a patient that he is at present treating.

Mrs. G. M., a 44-year-old nulliparous woman, was first seen in June, 1955, complaining of marked frequency, dysuria, and difficulty in voiding of several months' duration. She had

been treated 5 years previously by another physician for a "badly infected diverticulum." No definitive operation was performed at that time because of the degree of infection, and she apparently became asymptomatic following conservative therapy.

A cystoscopic examination showed some tumor tissue projecting through three openings in the floor of the urethra. There was a palpable mass about 5 by 7 cm. to the left of the midline beneath the urethra and within the diverticulum sac. Ureteral catheterization and retrograde pyelograms showed no involvement of the upper urinary tract.

The diverticulum and tumor mass were removed surgically, and, at that time, some thickening of the tissue beneath the trigone was found, and a complete excision of the neoplastic tissue was deemed impossible except by radical operation which she repeatedly refused. Epidermoid carcinoma, Grade III, was the pathological diagnosis.

A month later radium implantation was made through the anterior vaginal wall with direction and guidance through the bladder which had been opened suprapubically. Eight 1 mg. radium needles at intervals of 0.8 to 1.0 cm. for a calculated dose of 3,500 r were used. She tolerated the procedure well and had an uneventful course for 9 months. At that time there seemed to be a recurrence of the tumor (1 by 2 cm.) to the left of the urethra, incorporated in the scar of the diverticulectomy. It was excised and has not recurred.

A year later a cystoscopic examination revealed no invasion of the bladder by any tumor tissue, but the floor of the bladder and the trigone area as well as most of the urethra, were all fairly well fixed. In October, 1957, she was placed on permanent suprapubic cystostomy drainage.

In January, 1958, a chordotomy was performed; satisfactory relief of pain on the left side and partial relief on the right were obtained.

The anterior vaginal wall and tissue below the urinary bladder was involved with neoplastic change. Recently a vesicovaginal fistula developed at the site of the radiation therapy.

The patient is still in a state of good general health and has no complaints except some discomfort of the right leg, 3½ years after therapy. The tumor has grown slowly and all evidence of metastasis is on a direct extension basis.

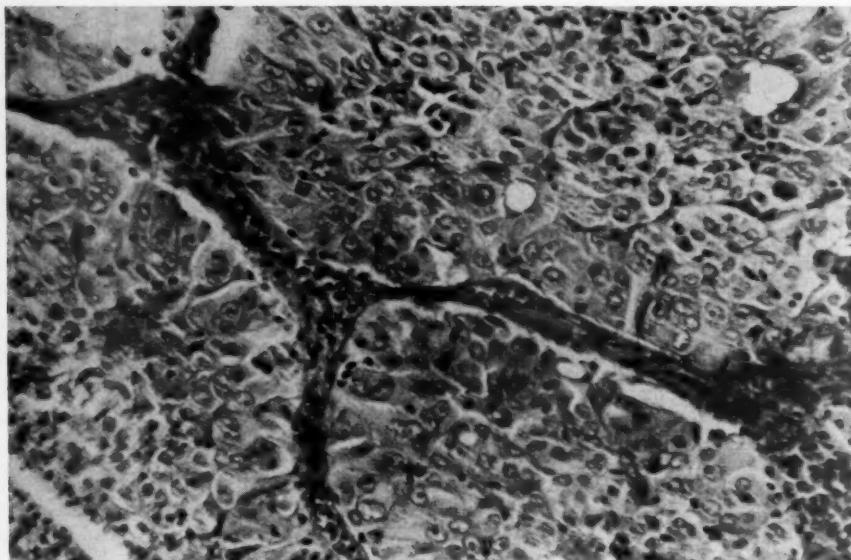


Fig. 1. Transitional cell carcinoma from biopsy specimen of suburethral mass.

We would like to add another case of this interesting and apparently rare entity to the literature.

Miss S. M., a 50-year-old saleswoman, was first seen in January, 1957, for diagnosis and treatment. Her chief complaint was spotting and a brownish vaginal discharge. She had had normal periods until 1953 when they became less frequent. In May, 1956, she began to bleed daily. In November, 1956, a curettage and cervical amputation resulted in benign pathological findings. The bleeding subsided, but spotting and a brownish leukorrhea continued.

The pertinent findings on physical examination were hypertension for which she was under treatment by her family physician. The cervix was healing well, but blood and a purulent leukorrhea were present in the os. The fundus and adnexa were normal.

At a second visit 2 weeks later, there was less leukorrhea. Granular tissue was still present on the cervix; it was cauterized. Blood was noted on the top of the speculum, apparently from the urethra, for the first time.

At a subsequent visit, induration was palpable in the paraurethral area, but she had no hematuria or frequency, only occasional nocturia. At no time did she complain of any urinary symptoms other than nocturia.

The cervix was unimproved, and purulent leukorrhea was still present in May, 1957. Pressure at this time on the urethra produced blood at the urethral meatus. Because of a suspicion of carcinoma, a genitourinary consultation was again suggested to rule out bladder or urethral disease.

On May 21, 1957, the patient was admitted to The Presbyterian Hospital for gynecological operation and urological investigation.

The last normal menstrual period began on March 29, 1957, and lasted 5 days. She complained of increasing fatigue and nocturia since November, 1956, and occasional urinary tenesmus, but no dysuria or hematuria. The blood pressure was 196/88.

Pelvic examination was unchanged except for a marked thickening of urethra which was palpated through the anterior wall of vagina. A mass the size of a walnut (3.5 by 2 by 2 cm.) was present between the bladder base and urethral meatus. Induration was present in the paraurethral tissue bilaterally and extending to bladder base.

Palpation of the suburethral mass caused a considerable amount of tissue to be extruded through the meatus. A specimen of this tissue was removed for biopsy. Cystoscopy disclosed an essentially normal bladder, and visualization of the urethra revealed an opening in the floor of the urethra distal to the external sphincter

and through which necrotic tissue protruded. Palpation of the mass against the cystoscope disclosed the mass again to be approximately the size of a walnut.

The pathological report of the biopsy showed: "The fragments have a somewhat papillary contour and are composed of neoplastic epithelial cells. The neoplastic cells are often somewhat elongated and exhibit oval and round nuclei. occasionally the cytoplasm seems vacuolated, but in general the histologic appearances are those of transitional type neoplasm. There is a moderate chronic inflammation in some sectors and some fragments are partially necrotic." Pathological diagnosis was transitional cell carcinoma in biopsy (Fig. 1).

Chest x-ray and intravenous pyelogram were negative for pathological condition or metastatic disease except for the finding of a double right calyceal system.

On June 3, 1957, a cervical biopsy was performed. Because of cervical stenosis, however, a curettage could not be completed. A small area exuding sanguineous fluid was noted for the first time in the anterior vaginal wall. Panendoscopy was much the same as described previously. The opening in the urethra was approximately 0.5 cm. in diameter; tumor tissue was visualized through this opening which represented a carcinoma in a diverticulum of the urethra. Twenty-four 1 mg. radium needles were inserted into the tumor and paraurethral tissue from the vaginal approach. The radium needles did not impinge upon the bladder or enter the urethra (as checked by panendoscopy).

The radiologist's note stated, "A typical Paterson-Parker application was used with one end uncrossed. If the radium is left in place 66 hours and 24 minutes, the volume of the tumor will receive 8,000 r." The radium was removed on schedule.

Postoperatively, the patient had an indwelling catheter in situ for 7 days. She was able to void spontaneously after the catheter was removed. She had no incontinence. Thiosulfil,* 0.5 Gm. 4 times a day, was given postoperatively and was continued upon discharge of the patient on the tenth postoperative day.

Initial follow-up examination revealed a moderate purulent leukorrhea. The urethral meatus was normal and the mass below the urethra was about the size of a quarter. She had

no urinary symptoms other than nocturia once nightly. The sulfonamide medication was continued. There was a diminution of the urethral mass at examination a week later.

Ten weeks later, the cervix appeared healed, although purulent leukorrhea was present. Some paraurethral thickening was noted, but there was no urethral discharge.

In November, 1957, panendoscopy disclosed a few polypoid excrescences at the vesical neck. The bladder was normal. The urethra showed a diverticulum opening on the floor. Minimal induration was present, and there was no evidence of tumor.

Since November, 1957, the patient has been checked at bimonthly intervals, and she has been asymptomatic. Vaginal examination has disclosed a persistent leukorrhea and minimal paraurethral induration.

Comment

The case presented is interesting for several reasons. The patient had had no genitourinary symptoms other than nocturia and was originally referred for a gynecological complaint. Even when the urethral bleeding and paraurethral induration were called to her attention she could recall no other genitourinary symptoms. It was 3 months before she consented to gynecological operation or urological investigation.

A mass the size of a walnut was then palpable in the anterior vaginal wall, and bloody discharge exuded from the meatus upon pressure on the sac. The gross diagnosis of carcinoma of a diverticulum of the urethra was confirmed by tissue biopsy.

Carcinoma of the urethra has been treated by one of four methods, two surgical, and two radiological. Recently, several small series^{4, 5} of cases have been reported with 50 per cent 5 year cure from the latter approach. In the 4 cases of carcinoma in a diverticulum that have been previously reported, the treatment has varied from simple excision of the diverticulum and tumor to irradiation and then excision to total urethrectomy and partial vaginectomy with cystostomy, all with apparently equal results.

Since there is no unanimity of opinion about treatment, the various approaches

*Thiosulfil, sulfamethizole, is a product of Ayerst Laboratories.

were discussed by the consultants and with the patient and her family physician. She elected to have radium treatment, and, if on follow-up the lesion did not respond, she would then consent to radical surgical therapy.

Fortunately, the radium implantation was successful, and she is well and asymptomatic 20 months after treatment.* This may be due to the radiosensitivity of the tumor or to the fact that it was recognized early and treated before there was any extension. It is interesting that this is the only case of this type that has been treated primarily by irradiation alone.

Summary

Four cases of carcinoma of a urethral diverticulum previously reported have been reviewed, and 2 additional cases have been presented.

Four of the patients are alive more than 3 years after the initial therapy. One patient is alive and well 2½ years after primary

radium therapy. One patient died 19 months after diagnosis and treatment.

Addendum. When the patient was examined cystoscopically and vaginally in February, 1959, the findings were unchanged. She was asymptomatic when examined again in June, 1959. The diverticulum was still present but biopsy of the epithelium was negative.

She was later readmitted with the complaint of leukorrhea and a slight bloody discharge from the vagina. Vaginal examination showed an increased induration of the paraurethral tissues and a purulent leukorrhea but no blood at this time. Urethral biopsy on Dec. 2, 1959, of the tissue now present in the diverticulum was reported as showing necrotic cells resembling cells from an earlier biopsy (transitional cell Ca).

On December 9, a cervical biopsy and conization and implantation of radium needles in the paraurethral area were performed. The cervical biopsy was reported as showing chronic cervicitis. The 12 radium needles remained in situ for 90 hours, giving a volume dose of 5,300 to 8,200 r (depending on the method of calculation). The postoperative course was uneventful and the patient was discharged from the hospital on the seventh day.

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*See "Addendum."

Primary adenocarcinoma of the female urethra

A review and report of 3 cases

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A D E N O C A R C I N O M A of the female urethra is recorded in the medical literature principally in the form of single case reports. In 1947 Walker and Huffman⁴⁰ collected 28 cases from the world literature. A number of these cases were reported only as a pathological diagnosis without pertinent clinical information. Since then, an additional 20 to 30 cases have been reported or referred to briefly.²⁴ The present communication is concerned with 41 reported cases, with significant clinical and pathological data, and 3 additional cases of my own.

The female urethra averages 25 to 45 mm. in length. The distal two thirds of the urethra is lined by nonkeratinized, stratified squamous epithelium. In the proximal one third there is a gradual transition to the transitional epithelium of the urinary bladder. The female urethra is homologous with that part of the male urethra which lies between the internal orifice and the opening of the prostatic utricle.^{18, 19} It is generally stated that in the female there is no equivalent of the penile portion of the male urethra, although Johnson believes that the shallow vestibule of the female is equivalent to that part of the male urethra between the prostatic utricle and the external urethral orifice. According to him, small glands, the lesser vestibular glands, develop in the anterior part of the vestibule and are homologues of the glands of Littré of the male.

*From the Department of Laboratories
Henry Ford Hospital.*

At the urethral orifice a number of paraurethral ducts open into the vestibule. Two of the larger ducts and their accompanying glands are known as Skene's ducts and glands. The paraurethral glands form a labyrinthine mass about the urethra and often extend not only around it but also along the greater part of the urethral canal (Fig. 1). In 1948 Huffman¹⁷ demonstrated in wax model reconstruction the detailed anatomy of these glands. In addition to the two major ducts, first described by Skene, which open into the vestibule, many ducts open into the distal one third of the urethral canal and a few into the middle and proximal parts of the urethra. They are lined by pseudostratified and stratified columnar epithelium in which occasional intraepithelial mucus secreting cells are present. At the termination of the ducts there are many small arborescent tubules and multiple-branched tubular glands, the lining cells of which vary from cuboidal to tall columnar (Fig. 2). These cells have abundant pale-staining cytoplasm and frequently show evidence of secretory activity. At times the glands are dilated, and inspissated secretions may simulate the secretions so frequent in the prostate.

Lymphatic vessels are numerous in the submucosa and in the periurethral tissues. The lymphatics of the female urethra are similar in arrangement to those of the prostatic bulbomembranous portion of the male urethra. Eisenstaedt states that the drainage of the proximal urethra is to the iliac and

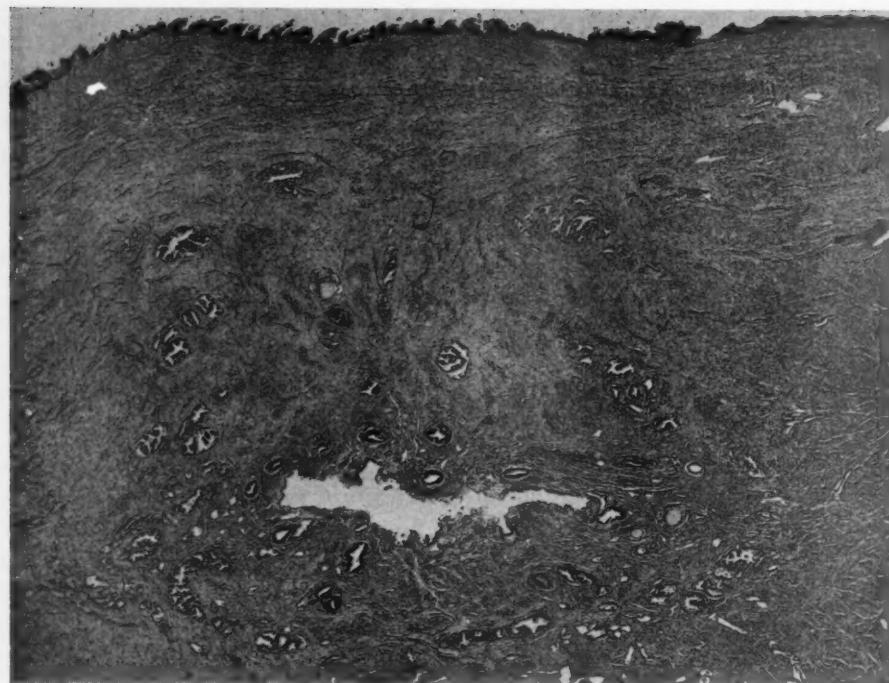


Fig. 1. Paraurethral glands surrounding urethral canal. ($\times 20$; reduced $\frac{1}{4}$.)

hypogastric lymph nodes, occasionally also to the node at the promontory of the sacrum. The lymphatic drainage of the distal urethra and the meatus is to the inguinal nodes.

Adenocarcinoma of the female urethra is said to arise from the paraurethral glands or glands of Skene. Virchow³⁹ assumed, on the evidence of histological similarity, that the paraurethral glands found in women in the neighborhood of the urethra are homologues of the male prostate. Korenchevsky and Dennison²² later suggested that these glands are not the counterpart of the whole prostate but only of its cranial and ventral lobes. They also investigated the hormonal dependence of these glands and suggested the name "female prostatic gland" instead of paraurethral glands since the former indicates clearly the nature and embryological origin of this tissue. In experimental animals they found these glands atrophic and were able to develop the "female prostate" into comparatively large structures by injections of androsterone and its derivatives. Estrogen had no obvious effect, the glands remaining atrophic. In the light of embryological origin it is not

surprising that adenocarcinomas of the female urethra resemble prostatic carcinomas. Theoretically, some adenocarcinomas may also arise from the urethral glands proper, like the glands of Littré in the penile portion of the male urethra. These carcinomas should arise in the immediate vicinity of the urethral orifice from the mucosa of the vestibule.

Approximately 10 per cent of carcinomas of the female urethra are adenocarcinomas, the majority being of transitional or squamous cell type (Table I).

Incidence

Adenocarcinoma of the female urethra is almost exclusively a disease of menopausal or postmenopausal women. Of the 44 collected cases (Table II) only 2 occurred before the fifth decade; 93 per cent of the patients were older than 45 years. The youngest was 26, the oldest 82 years of age. The average age in 42 cases was 56.6 years. Of the 23 patients whose marital status was known, 21 were married, 2 were single. There does not seem to be any relationship

Table I

	Squamous or transitional cell carcinoma	Adeno- carcinoma
von Mikulicz-Radecki	9	1
Hamann and Göbel	14	2
Bruntsch	8	1
Ritter	24	3
Staubitz	30	2
Monaco	19	2
Henry Ford Hospital	10	1

between multiparity and the occurrence of adenocarcinoma. Of 12 patients in which the parity was stated, 3 were nulliparas, 4 primiparas, and 5 multiparas. There does not seem to be any racial predilection; of the 23 cases in which race was mentioned, 18 patients were white and 5 were Negro.

Symptoms

The onset is usually insidious, the symptoms including hematuria, dysuria, bloody discharge, incontinence, and local pain. Only 3 of 41 patients were aware of a growing tumor. Pain, emaciation, and weight loss are late symptoms. Urethral obstruction with retention and uremia occurred in 15 per cent of the patients. The duration of symptoms ranged from a few weeks to several years; the majority of patients have a duration of symptoms of less than 6 months.

The majority of adenocarcinomas of the female urethra involve the distal urethra only and are usually visible at the meatus. There is no authenticated case in which the carcinoma arose in the proximal urethra or involved the proximal urethra only. Of the 40 cases for which precise location is reported, in 29 (72 per cent) there was involvement of the distal urethra only and in 11, involvement of the entire urethra.

Survival

In many cases in this series the period of observation has been too short to be useful for analytical purposes. In 8 cases 5 year survivals have been recorded. In 7 of these 8 cases the tumor was present either at the

external meatus or involving the distal urethra only. In one case the location is not stated. Metastases of adenocarcinoma of the female urethra are not infrequent. Most of the adenocarcinomas of the female urethra drain into the more superficial lymphatics of the vulva and thereby to the nodes of the inguinal region.

The inguinal nodes were not involved in 6 of the 8 patients with a 5 year survival. In 2 cases the status of the inguinal glands was not stated. Six of the 8 patients were treated by local resection and radium and/or roentgen therapy or by radiation alone. Only 2 were treated by surgical excision alone.

Twelve patients are known to have died. Three of these died as the result of operation in the immediate postoperative period. Seven of the remaining 9 showed involvement of the entire urethra and 2 of the distal urethra, when first observed.

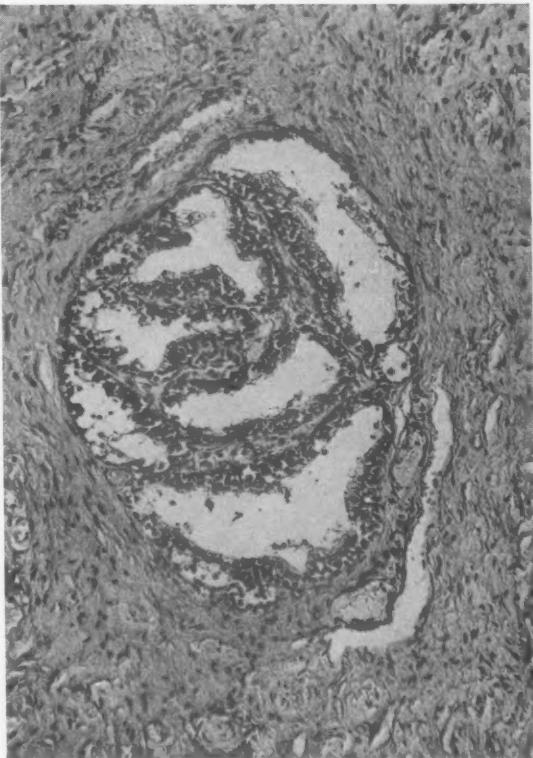


Fig. 2. Paraurethral gland lined by cuboidal to tall columnar mucus-secreting cells. ($\times 150$; reduced $\frac{1}{2}$.)

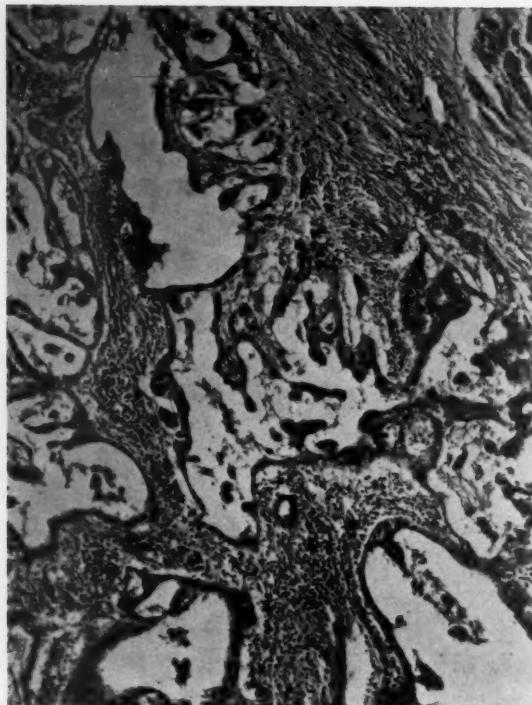


Fig. 3. Case 1. Adenocarcinoma of paraurethral glands. ($\times 105$; reduced $\frac{1}{3}$.)

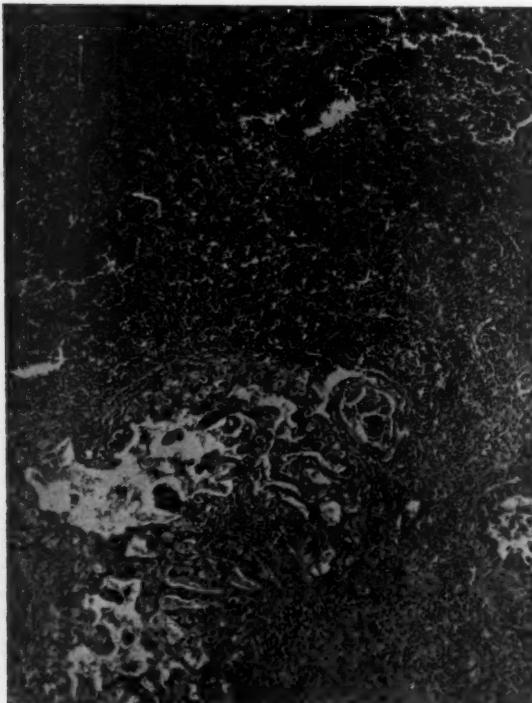


Fig. 4. Case 1. Secondary adenocarcinoma in regional lymph node. ($\times 105$; reduced $\frac{1}{3}$.)

In 3 untreated patients death occurred within 2 days to 4 months. The treated patients survived from 2 months to 2½ years. Inguinal gland metastasis was present in 4 cases, not present in 2, and not stated in 3 cases. Autopsy reports were available in only 2 cases (Cases 20 and 33). The first patient died from carcinomatosis 2½ years after treatment, with metastases to iliac, para-aortic, and bronchial lymph nodes, lung, liver, ovary, and lumbar spine and pelvis. The second showed pulmonary metastasis.

Case reports

Case 1. A. C., a 52-year-old married Negro woman, was first seen at Norfolk General Hospital in 1933. Anteroposterior repair, cauterization of the cervix, appendectomy, left oophorectomy, resection of the right ovary, and a round ligament suspension operation were performed. In 1945 the patient returned because of pain after urination. A stricture of the urethra was found and dilated some 9 times in the ensuing year. The patient was next seen in 1951 because of urinary difficulties and hematuria of about 3 months' duration. She had syphilitic aortitis and systolic hypertension (210/94). A beefy red mass approximately 2½ by 3 cm. occupied the anterior urethra, producing obstruction. The meatus was ulcerated. Cystoscopy revealed induration along the course of the urethra. The vesical neck was clear. In both inguinal regions shotty hard nodes were palpable. Biopsy revealed an adenocarcinoma which was thought to have arisen from paraurethral glands. Both ureters were transplanted into the sigmoid colon. Six weeks later a total hysterectomy, right oophorectomy, and total cystectomy with removal of the urethra were performed. The patient received a total of 1,350 r of deep radiotherapy postoperatively; she died 3 weeks after termination of therapy. Autopsy was not performed.

Gross pathological examination revealed an ulcerated papillary growth (2 by 3 by 3 cm.) on the left posterior lateral wall of the anterior urethra. The surrounding structures were indurated.

Microscopic examination showed an adenocarcinoma of the female urethra with invasion of the base of the bladder and periurethral tissue and metastasis to regional lymph nodes. Clumps and branching strands of tumor cells having a papillary configuration and growing in a gland-

like pattern infiltrated the urethra and periurethral structures. These were for the most part polygonal and large with oval or rounded vesicular nuclei with prominent nucleoli. In some areas the cells were low cuboidal or columnar; vacuolization was often conspicuous (Fig. 3). Few mitotic figures were seen. The tumor in the lymph node was similar in appearance to the primary growth (Fig. 4).

Case 2. A. R., a 50-year-old married Negro woman, was first seen at Norfolk Community Hospital in 1956 with a chief complaint of passing blood through the urethra for the preceding 4 to 6 months. The patient had seen several doctors and biopsy was advised but delayed by the patient. At the time of examination, the urethra was thickened throughout its length. The serological examination was negative. The inguinal lymph nodes were palpably enlarged. Biopsy of the urethra showed a well-differentiated adenocarcinoma. An excised inguinal node contained metastases. The patient was treated by radiotherapy but died with clinical evidence of widespread metastasis one year later. Autopsy was not performed.

Gross pathological examination of the biopsy specimen revealed an irregular piece of red-brown tissue measuring 12 by 6 by 4 mm. A lymph node, measuring 10 by 8 by 3 mm., grossly replaced by gray-white tissue, was also received.

Microscopic examination of the biopsy specimen showed a papillary growth of great uniformity (Fig. 5). The papillae consisted of delicate fibrovascular stalks and were lined by tall columnar cells with clear cytoplasm and basally located hyperchromatic nuclei of oval to spindle shape. The cells were crowded and hyperchromatic. The lymph node showed almost complete replacement by similar tumor tissue (Fig. 6). The cytoplasm of numerous cells in the biopsy specimen and in the lymph node was mucicarmine positive.

Case 3. E. W., a 55-year-old married white woman, gravida ii, para ii, was first seen at Henry Ford Hospital in 1951 because of a periurethral abscess which was incised and partially excised. Histological examination did not reveal evidence of tumor. She gave a history of episodes of urgency, frequency, burning, dysuria, and difficulty in voiding for 19 years prior to her first admission. Repair of a cystocele and rectocele had been carried out 2½ years before admission. Between 1951 and 1955 the urethra was dilated periodically, a Marshall-Marchetti

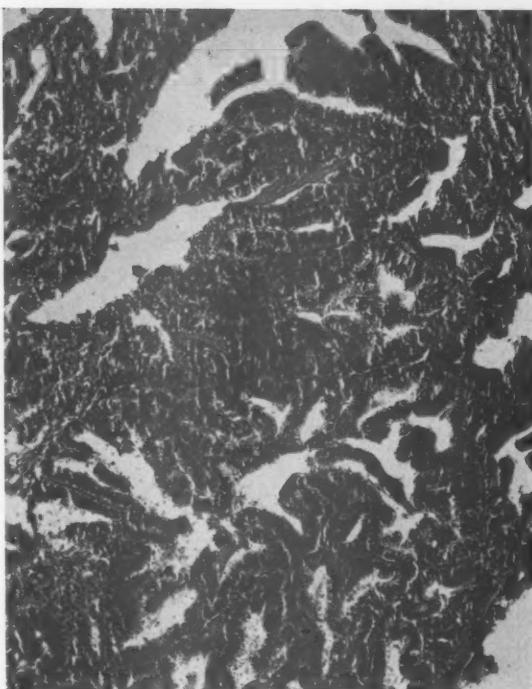


Fig. 5. Case 2. Adenocarcinoma of paraurethral glands. The tumor consists of a papillary growth of great uniformity. ($\times 105$; reduced $\frac{1}{3}$.)

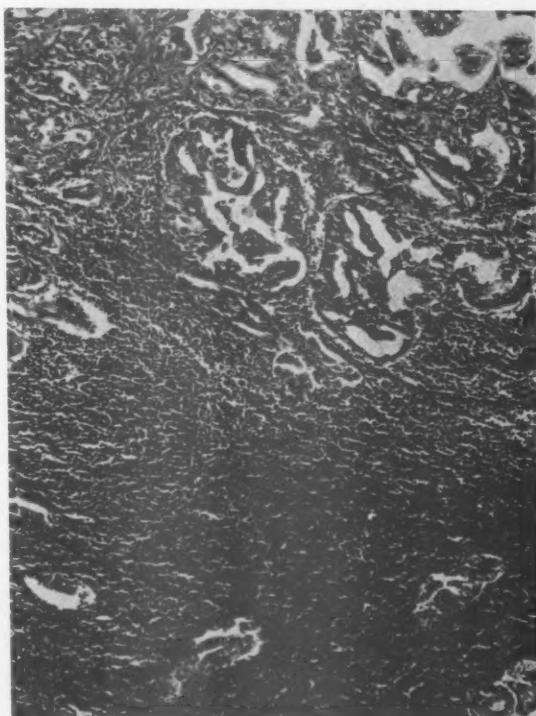


Fig. 6. Case 2. Secondary adenocarcinoma in inguinal lymph node. ($\times 105$; reduced $\frac{1}{3}$.)

Table II. Adenocarcinomas of female urethra

Case No.	Author and year	Age, race, marital status	Symptoms and clinical diagnosis	Gross description and location	Microscopic appearance	Treatment and survival	Metastasis to inguinal lymph glands
1	Battle, ¹ 1901	58; married	6 weeks' dysuria and pain	Hard, ovoid, 2½ inch tumor involving urethra in its entire length	Papilliferous columnar cell carcinoma	Excision of urethra cystostomy; well 9 months later	No inguinal gland involvement
2	Ward, ⁴¹ 1903	51	Foul discharge	Only distal urethra involved; urethrovaginal fistula	Adenocarcinoma	Excision followed by x-ray therapy	Not stated
3	Knoll, ²¹ 1905	68	Severe genital bleeding, dysuria, frequency, and foul discharge	Walnut-sized (? 3 cm.) tumor below and to right of urethral meatus, involving only anterior urethra	Glandular carcinoma	Excision; 6 months later no recurrence	No inguinal gland involvement
4	Boyd, ² 1906	51; married	Pain and growing lump at urethral orifice for 9 months, hematuria	Tumor in anterior urethra, not involving posterior urethra	Columnar cell carcinoma, papilliferous	Excision of anterior urethra; alive and well 5 years later; incontinence	No inguinal gland involvement
5	McMurtry, ²⁵ 1908	47	Dysuria, caruncle growth persisted and increased after excision	Chestnut-sized (? 3 cm.) tumor from urethral floor, protruding from meatus; bled easily	Adenocarcinoma	Excision; bladder and inguinal glands involved 15 months later	Inguinal glands involved 15 months later
6	McMurtry, ²⁵ 1908	26	Dysuria, tumor removed twice before; painful growth, occasional bleeding	Small sessile growth protruding from meatus	Transition from adenoma to adenocarcinoma	Excision	Not stated
7	Poppel, ³¹ 1908	45	Frequency and tumor for 5 years; profuse bleeding on trauma	Hen's egg-sized tumor (6 cm.), cauliflower-like, meatus at summit of tumor	Adenocarcinoma papillare et gelatinosum	Excision; no recurrence 9 months later	Inguinal glands not palpable
8	von Englehardt, ⁹ 1912	51; white	Symptoms of few months' duration	Tumor involved entire urethra and trigone, encircled urethra	Adenocarcinoma primary	Excision	Inguinal glands enlarged (clinically)
9	Roberts, ³² 1912	49; white	Hematuria and cystitis	Entire urethra involved by tumor	Columnar cell carcinoma	Inoperable, died 4 months later	Not stated
10	Duncan, ⁸ 1925	50; married; para 0	Frequency, dysuria several months; acute retention 4 days prior to admission	Ulcerative erosion lower portion of external urethral orifice; entire urethra indurated	Colloid carcinoma	Excision of urethra; death 5 days after operation, in uremia	Not stated

ried;
para 0 several months; acute portion of external urethral orifice; entire urethra indurated

retention 4 days prior to admission

11	Von Mikulicz-Radecki, ²⁸ 1931	55; white; single	Not stated	Urethral meatus surrounded by tumor extending to midurethra	Adenocarcinoma	Radium and roentgen therapy; died 5 years later; cause not stated
12	Von Mikulicz-Radecki, ²⁸ 1931	31; white; married; gravida ii	Incontinence, vaginal bleeding, pregnant 9 months, uremia	Chestnut-sized (? 3 cm.) tumor, ulcerated off urethral meatus, involving only anterior urethra	Adenocarcinoma, papillary-columnar	Excision followed by radium; well 2 years later
13	Menville and Counseller, ²⁷ 1934	45; white; married; para iii	Prolapse 23 years prior; peculiar carriage at meatus 14 years prior; dysuria, bloody mucoid discharge 6 months	7.5 cm. round mass, bleed easily; limited to anterior urethra; no involvement of rest of urethra	Mucoid carcinoma Grade IV	No inguinal gland involvement
14	Menville, ²⁶ 1936	63; Negro; single	3 months dysuria	Pedunculated soft mass protruding from urethra arising in anterior urethra	Adenocarcinoma	Excision and fulguration; no follow-up
15	Menville, ²⁶ 1936	58; married; para 0	Dysuria, frequency, difficulty in urinating; tender growth noted	2 cm. mass encircling urethral meatus	Adenocarcinoma	Excision and fulguration; well 7 months later; no further follow-up
16	Menville, ²⁶ 1936	63; white; married; para i	Dysuria, pain on urination for 6 months	Olive-sized mass (2 by 1 by 1 cm.) anterior urethra	Adenocarcinoma	Transplant of both ureters; died 3 days postoperatively
17	Kaplan, ²⁰ 1938	57; married	Vaginal discharge and pain in lower left pelvis	Large irregular mass surrounding the urethral meatus and invading the vaginal wall	Adenocarcinoma	Roentgen therapy followed by interstitial radium to local lesion; x-ray to inguinal glands; died 2 months later
18	Sala and Levine, ³⁶ 1940	72; Negro	Pain, burning 6 months, incontinence and vaginal spotting	Urethra obstructed by infiltrating tumor, entire length	Adenocarcinoma	Uremia on admission; No inguinal gland involved in pulmonary edema
19	Graves and Guiss, ¹⁴ 1941	44; white; married; para i	Vaginal bleeding; adenomatous polyp removed; 4 years later recurrence adenocarcinoma	Papillary appearance of urethral meatus; limited to distal urethra	Adenocarcinoma	Interstitial radium; well 2 years, 4 months later

Table II—Cont'd

Case No.	Author and year	Age, race, marital status	Symptoms and clinical diagnosis	Gross description and location	Microscopic appearance	Treatment and survival	Metastasis to inguinal lymph glands
20	Graves and Guiss, ¹⁴ 1941	56	4 years renal pain and dysuria; 1 year hematuria; one month prior complete retention	Circumscribed mass involving entire urethra and bladder neck	Adenocarcinoma, papillary type	Excision and x-ray; died from carcinoma 2½ years later; necropsy: metastasis to iliac, para-aortic, bronchial lymph nodes, lung, liver, ovary, and lumbar spine	1½ years later inguinal gland metastasis
21	Nichol, ³⁰ 1941	66; married	Vaginal spotting, dysuria some months	Fungating tumor large bean-sized (? 1½ cm.) at urethral orifice, ulcerated surface, no fixation	Adenocarcinoma, columnar cell	Radium and roentgen therapy of urethra and deep glands; patient well after 6 years	No inguinal gland involvement (clinically)
22	Cuscaden, ⁵ 1944	49 married	History of pain and hemorrhage	Not stated	Adenocarcinoma	Radium therapy; patient alive 2 years, 3 months later	Not stated
23	Göbel and Vonessen, ¹² 1947	49; white; married; para iii, abortus ii	Noticed tumor for 18 months; 6 months incontinence, hematuria, dysuria	Large pedunculated polyp from mucosa of distal urethra, protruding from meatus	Adenocarcinoma	Local resection, radium and roentgen therapy; alive and well 6 years later	No inguinal gland involvement
24	Buschke and Cantril, ⁴ 1948	57; white	Spotting for 2 years; hemorrhage 1 month prior to admission	Mushy papillary growth from external meatus	Adenoacanthoma	Roentgen therapy 5,200 r; well 5 years, function good	Not stated
25	Buschke and Cantril, ⁴ 1948	68; white	Pain and partial obstruction for 5 months; cauterization 3 months	Flat ulceration and induration of posterior wall, distal and middle urethra	Adenoacanthoma	Roentgen therapy 4,600 r; well 4 years; incontinence	Not stated
26	Buschke and Cantril, ⁴ 1948	65; white	Bleeding for 2 months; 1 by 1.5 cm. tumor at external urethral orifice; removal of tumor with recurrence	Adenoacanthoma	Roentgen therapy 5,000 r; no follow-up	Not stated	

27	Seng and Siminovitch, ³⁷ 1948	Married	Anuria, hematuria dysuria, frequency, nocturia for 9 months, caruncle removed; 14 months later	Raspberry type of growth protruding from urethral meatus; 5 months later 5 mm. recurrence	Adenocarcinoma, papillary type	2 and 3 years later recurrences all treated by excision; well after 6 years	Enlarged but not involved
28	Hamilton and Leach, ¹⁶ 1951	53; married	Vaginal bleeding 1 year; 9 cm. diverticulum middle urethra with a 4.5 cm. tumor within it	Tumor; 8 months later recurrence in vagina; 5 months later recur- rence in vagina and urethra	Adenocarcinoma arising in urethral diver- ticulum	Excision and roentgen therapy plus radium therapy; no follow- up	Inguinal lymph nodes not in- volved histologi- cally
29	Riches and Cullen, ³⁴ 1951	74	Bloody discharge and dysuria 8 months	Papillomatous growth with narrow base at urethral orifice	Adenocarcinoma, columnar cell	Excision, radium; 14 months later re- currence; excision (diathermy); alive and well 6 years	No inguinal gland involvement (clinically)
30	Riches and Cullen, ³⁴ 1951	55	Caruncle excised 5 and 3 years earlier	Excision of new recurrence Columnar cell carcinoma	Radium implant; well after 10 years	No inguinal gland involvement	
31	Deinhardt, ⁶ 1951	67; white	Anuria, uremia	Ulcerated tumor at exter- nal orifice obstructing urethra	Adenocarcinoma (gelatinous carcinoma)	Died in uremia 2 days after admission	Not stated
32	Ritter, ³⁵ 1953	74; white; married; gravida i, para i	Duration of symptoms 3 months	Papillary 4 cm. mass along floor of urethra and anterior vagina	Adenocarcinoma	Radium therapy; died 12½ months later with frozen pelvis	No inguinal gland involvement
33	Ritter, ³⁵ 1953	60; white; married; para i	Duration of symptoms 3 months	2.5 by 5 cm. mass of the floor of meatus and anterior urethra	Adenocarcinoma	Pelvic evisceration except rectum; died 2 years, 1 month later with carci- nomatosis with pul- monary metastasis	Inguinal gland metastasis 4 months after diagnosis
34	Ritter, ³⁵ 1953	65; white; para 0	Duration of symptoms 1 year	2 by 3 cm. mass at meatus involving entire urethral and anterior vagina	Adenocarcinoma	Pelvic evisceration except rectum; no recurrence 4 months later	No inguinal gland metastasis
35	Glenn, ¹¹ 1953		Frequency, burning, followed by aching pain for 8 months	Indurated nodular mass around urethra proximal to meatus	Adenocarcinoma	Radiation therapy; died 12 months later with extensive carcinomatosis	No inguinal gland metastasis

Table II—Cont'd

<i>Case No.</i>	<i>Author and year</i>	<i>Age, race, marital status</i>	<i>Symptoms and clinical diagnosis</i>	<i>Gross description and location</i>	<i>Microscopic appearance</i>	<i>Treatment and survival</i>	<i>Metastasis to inguinal lymph glands</i>
36	Delaimi, ⁷ 1954	53; white; married; para iii	Hematuria, burning at voiding for 8 months	Easily bleeding, mushroom-like tumor at meatus	Adenocarcinoma	X-ray therapy; well after 2 years	Not stated
37	Gonzales and Kaufman, ¹³ 1954	55; Negro	Leukorrhea and blood loss for some time	Hazelnut-sized (?) tumor inferior border of meatus, irregular surface	Adenocarcinoma	Extrication of urethra, urethral plastic; died of intercurrent illness 3 months later	Not stated
38	Bruntsch, ³ 1954	69; white; married; para iv	Bloody urethral discharge for several months; incontinence	Polypoid plum-sized (? 2.5 cm.) tumor arising from lower urethra	Adenocarcinoma	Radium therapy; surgical resection of tumor; patient well 7 years later	No inguinal gland involvement
39	Roth, ³³ 1955	66	Difficulty voiding, urinary retention, uremia	Urethra indurated with tumor mass	Adenocarcinoma	Refused treatment; died 3 months later in uremia	Not stated
40	Roth, ³³ 1955	82	Acute urinary retention	Entire urethra involved	Adenocarcinoma	Transurethral resection; patient did not return	Not stated
41	deMaurizi, ²³ 1956	55	Dysuria, tenesmus, hematuria	Lentil-sized mass (? 5 by 5 by 2 mm.), irregular, hard, protruding from meatus, anterior urethra	Adenocarcinoma, carcinoma microalveolare	Surgical extirpation; no follow-up	Not stated
42	Knoblich, 1959	52; Negro; married	Dysuria and hematuria 3 months	Ulceration of urethral meatus 2½ by 2½ x 3 cm. anterior urethra	Adenocarcinoma, papillary type	Vesicourethrectomy, radiation 1,250 r total; died 3 weeks after treatment	Metastasis to perirectal glands
43	Knoblich, 1959	50; Negro; married	Hematuria, dysuria 4 to 6 months	Urethra thickened in its entire length	Adenocarcinoma, papillary type	Radiotherapy alone; died with evidence of metastasis one year later	Inguinal gland metastasis
44	Knoblich, 1959	55; white; married	19 year history of dysuria, diverticulum previous to development of carcinoma	? 3 by 3 by 2 cm. tumor polypoid, lower half of urethra	Adenocarcinoma	Cystohysterourethrectomy, radium implants metastasis to vagina 3 years later; patient well for 4 years	No inguinal gland involvement

operation was performed, and a diverticulum was excised from the mid-urethra. Microscopic examination did not reveal evidence of tumor. In 1955 the patient presented with a urethral prolapse with sloughing of the protruding portion of the lower half of the urethra. At the external meatus there was a polypoid, cauliflower-like lesion which was partially necrotic and which bled easily. Biopsy revealed an adenocarcinoma thought to arise from Skene's glands. A total hysterocystourethrectomy and clitoridectomy with excision of labia minora was performed. The ureters were reimplanted into an isolated segment of ileum. An inguinal lymph node was excised. Metastasis was not seen. In 1958 a metastatic nodule (3 by 4 by 2 cm.) was excised from the vagina. At this time the patient was treated by radium implantation. The tumor beneath the symphysis pubis in the vaginal mucosa regressed completely after radium therapy. She has remained asymptomatic, without evidence of lymphadenopathy. Vaginal and rectal examinations were negative.

Gross pathological examination of the biopsy specimen showed a brown-black spherical piece of tissue measuring 1 cm. in diameter.

Microscopic examination showed glandular structures of varying size embedded in connective tissue. The glands were lined by a crowded irregular columnar epithelium which showed frequent papillary infolding. The individual cells had either clear or vacuolated cytoplasm and irregular hyperchromatic nuclei (Fig. 7).

The operative specimen showed tumor extending into the proximal urethra. The inguinal lymph node was free of tumor. The bladder and uterus were unremarkable. The metastatic lesion in the vagina removed 3 years later showed a somewhat less well differentiated tumor.

Comment

The cases reported are consistent clinically and pathologically with those previously recorded. Adenocarcinoma of the female urethra usually occurs in menopausal or postmenopausal women and shows no apparent racial predilection. It arises from paraurethral glands almost exclusively in the distal urethra.

The symptoms are those of urinary difficulty, frequently including hematuria. Initial spread is to the inguinal lymph nodes but distant metastases including bony metastases

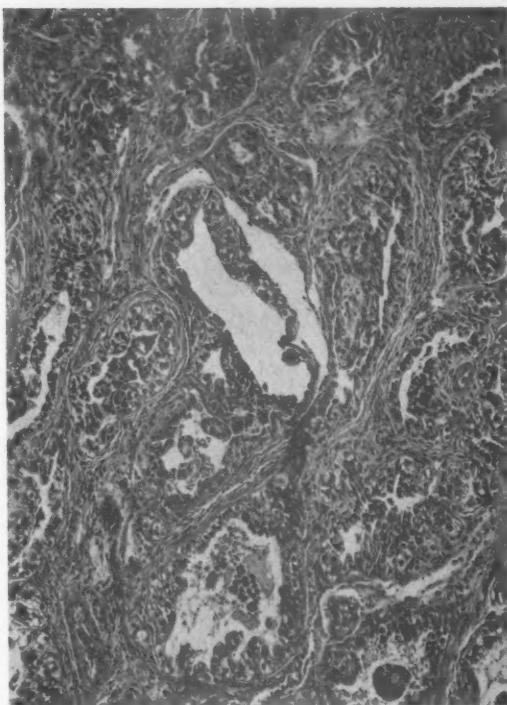


Fig. 7. Case 3. Adenocarcinoma of paraurethral glands. The glands are lined by a crowded irregular columnar epithelium. ($\times 105$; reduced $\frac{1}{3}$.)

occur. Fourteen patients (including 2 reported here) are known to have died; 8 have survived 5 years or more free of clinical evidence of disease.

Local resection and radium or roentgen therapy to the tumor and inguinal nodes have been the most frequently used methods of treatment. Involvement of the entire urethra and inguinal node metastasis are poor prognostic signs. The experimental demonstration that the paraurethral glands respond to androgenic hormones by hypertrophy as does the male prostate suggests the possibility of supplementing surgical and radiation therapy by administration of estrogens.

Summary

Forty-one cases of adenocarcinoma of the female urethra reported in the literature with adequate clinical and pathological data are reviewed. Three additional cases are reported. Two patients died shortly after initial treatment, one with widespread metastases.

The third patient survives without clinical evidence of tumor 4 years after initial surgi-

cal therapy and one year after radiation treatment of a vaginal metastasis.

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Cavernous lymphangioma of the uterus

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VASCULAR tumors of the uterus are rare. Only 8 true examples of cavernous hemangioma of the uterine body have been recorded.¹ Uterine lymphangiomas are rarer still. A search of the literature yielded only 2 previous cases.

Umeda and Ro² described a typical cavernous lymphangioma of the uterus as an incidental autopsy finding. This was a non-encapsulated mass, measuring 1 cm. across, situated near the right cornu in a 77-year-old woman.

Löffler³ observed another typical example in a woman of 60, in whom a vaginal hysterectomy was carried out because of a whitish vaginal discharge and prolapse. The uterus was enlarged to the size of a "small fist" and was knobby in outline and yellowish in color. On section of the fundus and part of the adjacent myometrium, an area measuring 4.5 by 4 cm. displayed a reticular pattern of indistinct outline and proved on microscopic examination to be a true cavernous lymphangioma.

This paper records the observation of a third case.

Case report

The patient, a 55-year-old nullipara, was seen in April, 1959, because of prolonged and irregular uterine bleeding for the preceding 3 years. The hemoglobin level was found to be 88 per cent and general examination was non-contributory. On vaginal examination the uterus was found to be anteverted, somewhat knobby,

From the Rivers Pathological Department, Camborne-Redruth Hospital.

and enlarged toward the right side of the pelvis. A diagnosis of uterine fibroids was made, and a total hysterectomy, bilateral salpingectomy, and right oophorectomy were carried out. No lymphangiectases were noticed either on external examination or during laparotomy. Progress was uneventful and the patient was discharged 2 weeks after operation.

Pathologic examination. The specimen received was an enlarged uterus, measuring 12 by 7.5 by 6 cm. and weighing 330 grams. Both tubes and the right ovary were attached. The cervix measured 4.5 cm. in length and was healthy. The uterine cavity was slightly elongated and lined by smooth endometrium; there were a number of small endometrial polyps in the fundus. There was a paracervical fibroid which measured 3.5 cm. in length, and the myometrium contained about 8 fibroids, measuring up to 3 cm. in diameter. Posteriorly, just above the level of the internal os, the uterine body bulged appreciably outward and here the tissues were soft and elastic in consistency. When

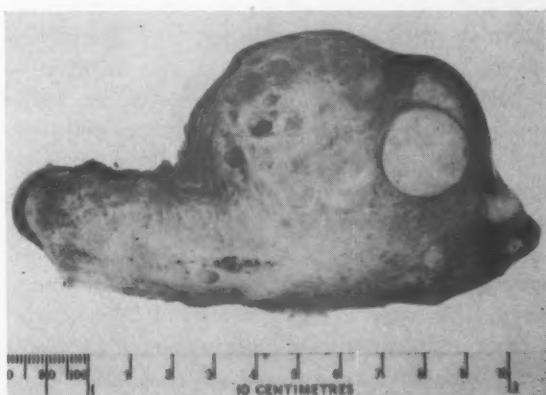


Fig. 1. Paramedian sagittal section through the uterus. Lymphangioma at top center.

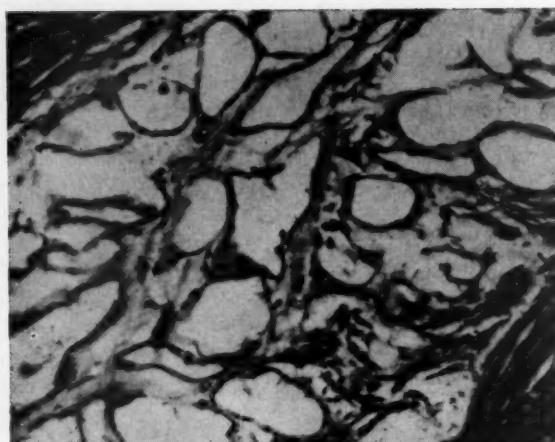


Fig. 2. Large number of lymph channels separating muscle fibers. (Hematoxylin and eosin. $\times 140$; reduced $\frac{1}{4}$.)

the organ was sliced sagittally this mass proved to be a poorly demarcated, nonencapsulated spherical area of honeycomb appearance, measuring 4.5 cm. in diameter, which was situated mainly within the myometrium and slightly eccentrically to the right, displaying innumerable small cysts measuring up to 0.5 cm. in diameter (Fig. 1). These were filled with a thin, mucinoid, transparent fluid and displayed a smooth, grayish, glistening lining. A margin of uninvolved uterine muscle, 1 cm. wide, separated this area from the base of the endometrium.

Histologic examination. Sections cut from the anterior uterine wall showed myometrium covered by moderately low endometrium with dilated glands and sessile endometrial polyps. Six large blocks were cut from the honeycombed area. The sections from all showed the myometrium to be riddled with numerous lymphatic channels (Fig. 2). There was no surrounding capsule; toward the periphery the lymphatic spaces became fewer in number and finally disappeared altogether. Below the serosa the lymphatic channels were of sinusoidal proportions and so closely spaced that muscle fibers virtually disappeared. Occasionally, the supporting connective tissue exhibited scattered small lymphoid aggregations. Although most of the lumina were empty, some still contained thin albuminous fluid. The inner lining was formed by a single layer of flat endothelial cells, although in some areas these were swollen and assumed a cuboidal shape (Fig. 3). Special stains, including Verhoeff stains for elastic fibers, did not show any additional features.

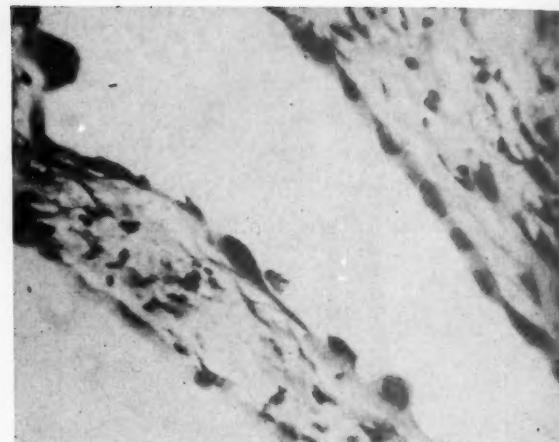


Fig. 3. Swollen endothelial cells lining lymph sinuses. (Hematoxylin and eosin. $\times 370$; reduced $\frac{1}{4}$.)

Pathologic diagnosis. (1) Cavernous lymphangioma; (2) multiple intramural fibroids; (3) endometrial hyperplasia and polyps.

Comment

Only a small number of lymphangiomas of the female genital tract have been recorded, and most of these involved the Fallopian tube.⁴ However, in this site the diagnosis has in many instances been erroneous, as the lesions constituted in reality adenomatoid tumors, an entity which has been recognized as such only recently,⁵ as, for example, the case reported by Sanes and Warner.⁶

A further possibility of confusion is the difficulty, occasionally encountered, in distinguishing lymphangiomas from a true lymphangioma. Partial blockage of the lymph flow is likely to occur in cases of pelvic obstruction, such as a fibroid uterus, but, in my experience, the dilated lymph vessels have, in these cases, been situated mostly subserously and were easily visible on inspection as one or more tortuous, thin-walled channels filled with thin, transparent fluid, and were thus quite different from a true angiomatic formation.

A fibroid undergoing cystic degeneration can also mimic a lymphangioma. These are usually well-circumscribed lesions however, and display, on microscopic examination,

degeneration of muscle fibers and much edematous hyaline fibrous tissue, which finally breaks down to form cystic spaces of irregular shape which are devoid of any endothelial lining⁷ and contrast sharply with well-formed lymph channels with their endothelial lining and smooth outline.

It may be more difficult to distinguish lymphangiectatic myomas from simple lymphangiomas. Dilated lymph vessels in the former will tend to be fewer in number, to be separated from each other by much fibroleiomyomatous tissue, and to be contained within the usually well-confined margins.

Most lymphangiomas are asymptomatic, and those of the uterus do not appear to be an exception. In the 2 previously recorded

cases the stroma displayed an increase in elastic fibers, to which Löffler² attributed the yellowish color of his specimen, but in the present case these were absent, and all 3 were solitary and of moderate size.

Summary

An asymptomatic intramural cavernous lymphangioma of the uterus is described which occurred in a 55-year-old woman. Only 2 previous cases were found in the literature.

I am most grateful to Professor R. A. Willis for confirming the diagnosis and reading the manuscript. Thanks are due to Miss Phyllis E. Coleman for assistance with the photography and to Mr. P. N. Simons for the clinical data.

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Uterine mesodermal mixed tumors

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ALTHOUGH lengthy and erudite contributions to the study of mesodermal mixed tumors have been made, as Shaw observed over 30 years ago,¹⁹ these lesions remain unusual and somewhat controversial both to the clinician and to the pathologist.

The purpose of this investigation is neither to give a historical review,^{5, 9, 11, 15, 19} nor to present a discussion of the terminology previously used in describing these tumors,^{14, 18} as excellent accounts of both are readily available. Rather, we wish to present our experience with the 6 cases of mesodermal mixed tumors encountered at Harper Hospital since 1930 and to add our views on histogenesis and criteria for microscopic diagnosis.

Presentation of data

The clinical and pathologic features of our cases are summarized in Tables I and II, respectively.

Although not statistically significant, our experience with the location of these tumors seems to concur with the view first expressed by Meikle,¹⁵ following his thorough review of published cases up to 1933, that the majority of mesodermal mixed tumors arise in the corpus rather than in the cervix as was previously thought.⁹ All of the lesions encountered were exclusively corporeal in origin with the exception of that in Case 4, which also had cervical and vaginal attachments.

The age incidence of from 36 to 71 years

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with an average of 54 years is comparable with the other reported figures for the corporeal occurrence.^{15, 21}

Abnormal vaginal bleeding was one of the presenting symptoms in 5 of our patients. In 2, the bleeding was preceded by a serous vaginal discharge. The remaining patient had only a short history of pain progressing from intermittent and colicky to constant and severe. If these symptoms are investigated as a matter of routine, delay in diagnosis would not seem to be a major problem in this condition. The short duration of symptoms is significant. They were present for 3 months or less in 4 out of the 6 cases studied.

In all but one patient physical examination revealed an enlarged uterus. In one (Case 1) the uterus seemed to be fixed. In 2 (Cases 1 and 2) there was lower abdominal tender-

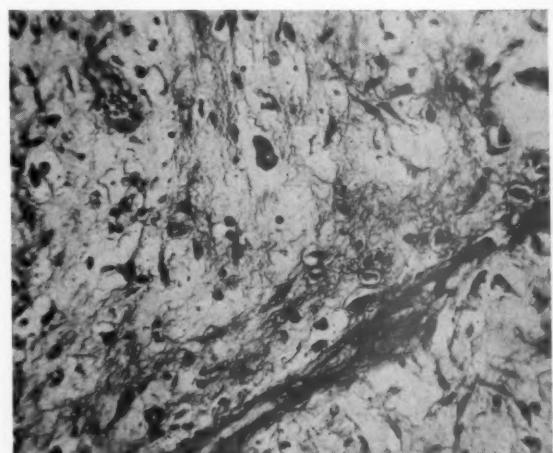


Fig. 1. Case 6. Mesodermal mixed tumor showing typical mesenchymatous tissue. Note the very delicate reticulum fibers. (Wilder's reticulum stain. $\times 140$; reduced $\frac{3}{4}$.)



Fig. 2. Case 6. Mesodermal mixed tumor showing granular rhabdomyoblasts. Nucleoli prominent. Cytoplasm fibrillary, granular, and eosinophilic. (Hematoxylin and eosin. $\times 700$; reduced $\frac{1}{2}$.)

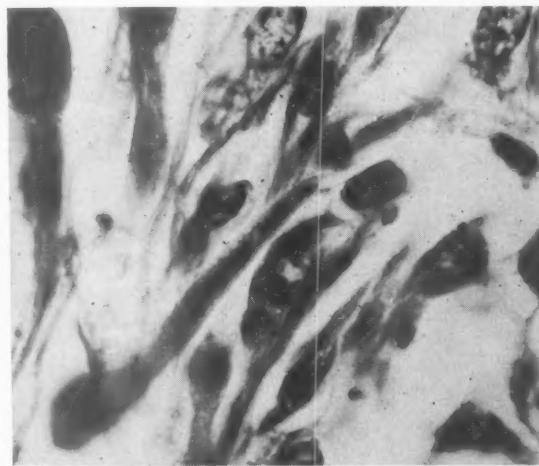


Fig. 3. Case 6. Mesodermal mixed tumor showing rhabdomyoblast with well-defined cross striations. No convincing cross striations could be demonstrated on routine hematoxylin and eosin preparations. (Mallory's phosphotungstic acid hematoxylin method for striations. $\times 700$; reduced $\frac{1}{2}$.)

ness. In 2 (Cases 5 and 6) the cervix was effaced and partially dilated. In 2 the tumor extended through the cervical os, presenting as a small bilobate gelatinous endocervical polyp in one (Case 3) and filling the vagina with a polypoid mass developing cervical and vaginal attachments in the other (Case 4).

There was nothing unusual in the obstetrical and menstrual histories with the exception of one patient (Case 5) who had had hypermenorrhea and endometrial polyps 25 years previously with a premature menopause at

34 years of age. Although reports of this tumor following irradiation for benign pelvic lesions are prevalent^{6, 18, 21} this was not the case in any of our group.

The one survivor (Case 5), 7 years to date, was treated by panhysterectomy and bilateral salpingo-oophorectomy followed by a full course of deep radiotherapy to the pelvis. The remaining 3 patients (Cases 2, 3, and 4) who survived operation all died with terminal marked abdominal distention and vomiting. All had local pelvic recurrence of the tumor. One of these (Case 3) received a full course of deep radiotherapy postoperatively. The other 2 (Cases 2 and 4) received terminal radiotherapy which was poorly tolerated and had no apparent palliative effect.

Three of the 4 therapeutic failures (Cases 1, 2, and 4) showed gross evidence of possible extrauterine involvement at the time of operation. In the first patient there were multiple dense utero-mental and utero-intestinal adhesions. In the second there was a thickening of the left round ligament and a left parametrial mass. In the third there were vaginal attachments of the tumor mass. In the remaining patients (Cases 3, 5, and 6), the tumor was limited to the mucosal region of the corpus at the time of diagnosis. There was no evidence of hematogenous spread in any of our cases.

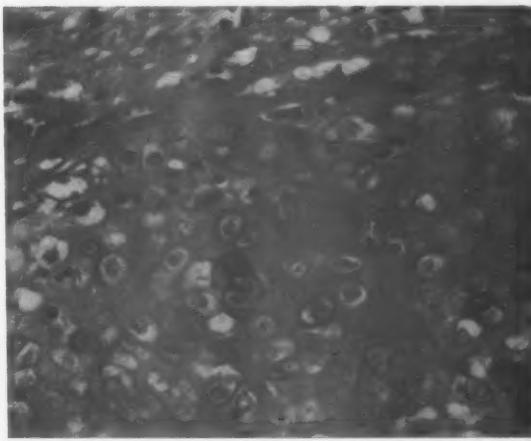


Fig. 4. Case 6. Mesodermal mixed tumor showing area of cartilaginous tissue. Notice the staining pattern of the cartilaginous matrix. (Lison stain. $\times 140$; reduced $\frac{1}{2}$.)

Table I. Summary of clinical data

<i>Case</i>	<i>Age</i>	<i>Symptoms</i>	<i>Physical findings</i>	<i>Menstrual and obstetrical history</i>	<i>Therapy</i>	<i>Results</i>
1 (1933), No. 93407	36	Weakness, 3 months; hy- permenses, 3 months; polymenorrhea, daily heavy flow, 1 month; nausea, 1 month	Slight abdominal disten- tion; left lower quad- rant tenderness; uterus enlarged and fixed, al- most filling pelvis, firm except for anterior softening	Menarche at 13 years; menses every 25 days with 5 day flow; gravida 0; married 13 years	Subtotal hysterectomy	Died 4 hours postopera- tively of surgical shock
2 (1937), No. 155144	52	Pain in left lower part of abdomen, colicky for 2 months, constant for 2 weeks	Pelvis mass size of 3 months' pregnancy, more prominent on the left side	Menarche at 14 years; menses every 28 days with 3-4 day flow; gravida x, para viii; menopause uneventful at 47 years	Pan hysterectomy; left sal- pingo-oophorectomy; resection of left round ligament and para- metrial fibrous mass; terminal x-ray therapy	Died in 6 months; local recurrence; marked abdominal distention
3 (1950)	51	Light vaginal spotting, 6 months; heavy spotting, 2 months	Uterus normal size; two grape-sized translucent polyps on single stalk projecting from cervical os, one purple in color	Menarche unknown; gravida i, para i; meno- pause at 49 years, un- eventful	Pan hysterectomy; bilateral salpingo-oophorectomy; postoperative deep x-ray to pelvis	Died in 1½ years; local recurrence; marked abdominal distention
4 (1951),* No. A 31625	58	Serous vaginal discharge, 3 weeks; vaginal spot- ting, 2 weeks; mass fill- ing vagina; 2 days	Polypoid mass filling vagina, attached to cer- vix and right fornix; uterus size of 3 months*	Menarche, unknown; gravida ii, para ii; menopause at 48 years	Pan hysterectomy with upper 2/3 vagina; bilat- eral salpingo-oophorec- tomy; x-ray 1 month later, discontinued	Died in 3 1/2 months; local recurrence marked abdominal dis- tention
5 (1952), No. A 138878	56	Serous vaginal discharge, 6 weeks; slight spotting for 2 days	Uterus the size of 3 months' pregnancy (routine examination 2 1/2 months earlier, very small postmenopausal uterus found)	Menarche at 15 years; menses every 30 days with 5-7 day flow; hypermenorrhea at 29 years, curettage; endo- metrial polyps at 30	Pan hysterectomy; bilateral salpingo-oophorectomy; postoperative x-ray to pelvis	Living; no evidence of recurrence
6 (1959), No. A 245169	71	Vaginal spotting, 8 months	Polypoid mass in cervical os, increased threefold in size in 6 weeks; uterus size of 2 months*	Menarche, unknown; multipara; menopause at 46 years	Died with myocardial infarct on way to operating room for biopsy	None

*Reported by Spademan and associates in 1952.

Table II. Summary of pathologic data

<i>Case</i>	<i>Gross pathologic findings</i>	<i>Microscopic pathologic findings</i>	<i>Extrauterine involvement</i>
1	Uterus in 3 portions aggregating 22+16+10 cm.; tumor origin anterior wall yellow, cystic, and hemorrhagic	Mesenchymatous connective tissue; granular rhabdomyoblasts; rare striated rhabdomyoblasts; spindle cells	Dense adhesions to omentum and intestine; no chest metastases on x-ray examination; no necropsy
2	Uterus 20+15+8 cm.; tumor origin not recorded; central degeneration of tumor mass	Mesenchymatous connective tissue; granular rhabdomyoblasts; striated rhabdomyoblasts, very difficult to demonstrate	Firm thickening of left round ligament; fibrous left parametrial intraligamentous mass; no necropsy
3	Uterus 6.5 by 4 by 3 cm.; subendometrial white gelatinous mass 1.6 cm. in diameter; normal-appearing cervix; tumor origin endometrium low posterior midline	Mesenchymatous connective tissue; spindle cells; granular rhabdomyoblasts; striated rhabdomyoblasts; fat cells; epithelial elements, malignant appearing in some areas, one fragment of papillary adenocarcinoma	None found at time of operation; frozen pelvis just prior to death; no clinical evidence of distant metastases; no necropsy
4	Uterus and upper 2/3 of vagina containing polypoid mass; uterine portion of mass 10 cm. in diameter; tumor origin endometrium low on right side	Mesenchymatous connective tissue very prominent; granular rhabdomyoblasts; striated rhabdomyoblasts; epithelium covering tumor simple cuboidal and stratified squamous; spindle cells; glandular elements; fat cells	Vaginal attachment of tumor mass; necropsy findings: right hemipelvic tumor involving ureter and sacral periosteum; periaortic, mesenteric, posterior mediastinal, and subpleural nodal involvement; vaginal recurrence
5	Uterus size of 3 months' pregnancy; lumen filled with polypoid mass effacing cervix tumor origin endometrium of posterior midline, yellow, soft, and cystic	Mesenchymatous connective tissue; spindle cells; granular rhabdomyoblasts; striated rhabdomyoblasts, very rare in occurrence; glandular elements	None
6	Uterus size of 6-8 weeks' pregnancy; lumen filled with polypoid mass effacing and dilating cervix to 2 cm. tumor origin endometrium anterior on the left of midline	Mesenchymatous connective tissue; granular rhabdomyoblasts; striated rhabdomyoblasts; cartilage; glandular elements; spindle cells not prominent	Necropsy findings: myometrium only superficially involved, no extrauterine tumor

Microscopically, mesenchymatous connective tissue was a feature of all our cases, being especially prominent in Cases 4 and 6 (Fig. 1). Giant cells and large spindle cells containing eosinophilic granular cytoplasm were found in all cases (Fig. 2). Cross-striated rhabdomyoblasts could be demonstrated in all, but many hours with oil immersion were spent on this specific task in Cases 2, 4, and 6. The demonstration was

facilitated, but still difficult, in Case 6 in which special stains were used (Fig. 3). Cartilage was found only in Case 6. Here it had the staining properties of young cartilage deficient in chondroitin-sulfuric acid suggested by Lison's stain¹² (Fig. 4). Glandular elements were prominent in Cases 3, 5, and 6. In Case 3 some of these had the microscopic features associated with malignancy (Fig. 5).

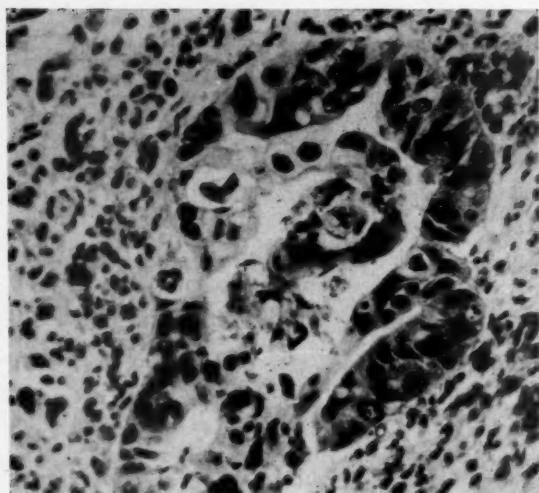


Fig. 5. Case 3. Mesodermal mixed tumor showing malignant-appearing glandular elements. In other areas of this tumor glandular structures have a benign appearance. (Hematoxylin and eosin. $\times 230$; reduced $\frac{3}{4}$.)

Comment

As was true at the turn of the century, there are still two major theories as to the origin of mesodermal mixed tumors: metaplasia, championed by Pfannenstiel,^{19, 23} and embryonal inclusion, by Wilms.²⁴ We concur with the opinion of majority of recent authorities who favor the latter,^{1, 4, 5, 8, 9, 14, 15} feeling that the embryological development of the region adds credence to this view.

In the very early embryo the nephrotome is directly adjacent to its corresponding somite, carrying a muscle and skeletal anlage.¹⁷ With growth there is a bulging of the nephrogenic tissue into the celomic cavity, forming the urogenital ridge.² The nephrogenic tissue in the dorsum of this ridge is that which earlier was in direct apposition to the somite.

It is in this area that the Müllerian ducts begin as a groove in the thickened epithelium (dorsolaterally on the urogenital ridge).² The cranial end of the groove remains open while more caudally there is an epithelial invagination to form a tube.⁷ Near the cloaca with the ventral swinging of the genital ridge, the laterally placed Müllerian ducts are brought together in the midline

and fuse, coming to a blind end in Müller's tubercle. This joins the urogenital sinus just caudad to the future trigone area. In the female, the sinovaginal bulbs combine with the caudal Müllerian system to form first the vaginal plate, then the vaginal tube.⁷ In the male, atrophy occurs with the only remnant of the fused Müllerian system being the male homologue of the vagina, the prostatic utricle.²

It seems entirely possible to us that small nests of multipotent mesodermal cells could be carried from the adjacent somite with the nephrogenic tissue into the urogenital ridge. From here they could be included in the epithelial inrolling which forms the Müllerian ducts and could be trapped without functional roll in the fused Müllerian system. It is this fused Müllerian system which is almost the exclusive site of origin of proved mesodermal mixed tumors, both in the female and in the male.^{1, 14}

Another interesting factor in mesodermal mixed tumors is the mucosal or immediately submucosal site of origin found in most reports. Linking this with the chronologic sequence of appearance (e.g., vaginal, infant; cervical, young adult; and corporeal, postmenopausal)^{4, 15, 21} it may be postulated that the malignancy arises in a period of mucosal quiescence shortly following marked epithelial activity (e.g., formation of vaginal plate in embryo,⁷ proliferation of the endocervical glands at adolescence,⁸ and cessation of hormonally stimulated endometrial changes at the menopause). Herein may lie the key to the onset of malignant change.

Criteria for the microscopic diagnosis of mesodermal mixed tumors have never been standardized. Thus, the most lenient certainly have overdiagnosed the condition while the strictest in all probability have omitted definite cases. We concur with those who feel that two or more heterotopic mesodermal elements are all that is necessary for the diagnosis,^{18, 22} as long as one of these elements is mesenchymatous connective tissue,¹ rhabdomyoblasts—striated^{8, 9} or granular^{6, 21}—or cartilage, since all 3 of these are unmistakable identifiable and represent

definitely heterotopic mesodermal elements. We see no difference in the clinical course of the reported cases meeting the above criteria and those meeting the more strict criteria of Läwen.⁸ His insistence on the presence of cross striations was associated with his concept of etiology⁸ and not related to biologic characteristics. As Läwen suspected⁸ and many others have emphasized since, there is little doubt that the large, strongly eosinophilic cells with the granular cytoplasm represent rhabdomyoblasts and should be accepted as such.^{6, 15, 21} The disappearance of both cross striations¹⁰ and granules¹⁶ in culture make one wonder if either would be found in tumors with anaplastic rhabdomyoblastic elements.

Summary and conclusions

1. We have summarized our experience with 6 mesodermal mixed tumors, only one of which has previously been reported.²⁰
2. The exceedingly short duration of symptoms in many of these cases makes it seem unlikely that earlier diagnosis will be

obtained, and to find a localized lesion is a matter of extreme good fortune as apparently the prognosis is not hopeless in this group.²¹

3. For the most part, mesodermal mixed tumors appear to be highly radioresistant. The spread is primarily by local extension and lymphatic dissemination. Thus, radical hysterectomy with gland dissection may offer a much better chance for cure in those patients who apparently have localized lesions, and repeated local excision with consideration of fecal diversion may be the best method of palliation.

4. It seems probable to us that these tumors originate in the mucosal region of tissues representing fused Müllerian anlage and that malignant degeneration is related to change in mucosal activity.

5. We feel that no clinical errors will be made if the microscopic diagnosis is based on the finding of two or more heterotopic mesodermal elements in the neoplasm, if at least one represents rhabdomyoblasts—striated or granular—mesenchymatous connective tissue, or cartilage.

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Selection of treatment for corpus cancer

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RECENT studies of the treatment of corpus cancer have developed along two major lines: (1) analysis of tumor biology and its relation to clinical staging and modes of extension, forms of data that may be used in selection of treatment and prognosis; (2) evaluation of extension of treatment over simple total hysterectomy whether this be by adjuvant radiation or more radical operation. The precision of many proposals and counterproposals has been hampered by the smallness of individual series, favoritism of one modality over another without supporting data of a critical nature, and unwitting selection of patient material by virtue of the position of the reporting clinic in its own medical community. Clinics favoring combined radiotherapeutic and surgical methods may have less "operability" selection than those favoring more radical surgical treatment, and those hospitals with a high percentage of patients drawn from the upper socioeconomic group will in general have a subtle but definite selection of earlier case material than will those clinics based on the large urban indigent hospital population.

We may be enabled to progress more rapidly in the solution of the problems encoun-

tered in the treatment of corpus cancer, then, if we have some classification common denominators that will allow us to compare material and critically evaluate its composition with the hope that the same benefit will be derived that has come from the use of the International Classification for Cancer of the Cervix.¹ Faulty though it may be and imprecise because of its clinical nature, the cervix cancer staging has brought great benefit to correlation and comparative studies of various modalities of treatment in this area.

With such a hope in view, we have studied our patients at the Sloane Hospital for Women and the Francis Delafield Hospital of the Columbia-Presbyterian Medical Center in the years 1938 to 1952 from the histologic, radiotherapeutic, and surgical points of view, and made an attempt to define our experience in a way that may be useful for comparative studies with other clinics. Our study utilizes 360 patients treated in our hospitals during these years, and perhaps its size may permit us certain observations that may bear significantly upon these therapeutic problems.

Contribution of the pathology laboratory

Histologic study of the surgical specimens offered prognostic data that seems to relate significantly to our treatment problems. It was interesting to note, as indeed others have observed, a striking decline in cure rate associated with: (A) lack of differentiation (Table I); (B) involvement of the cervix (Table II); (C) deep myometrial invasion (Table III); and (D) involvement of the

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ovary (but not tube where mere geographic extension does not have the same grave importance that ovarian metastasis does (Table IV).

It seems clear that selection of some patients for more extended surgical or radiotherapeutic treatment must be based on these considerations if we are to improve our present cure rate in these unfavorable areas. This may be done in a reasonably accurate way if these criteria are applied to staging.

Contribution of clinical staging

A derivative clinical classification of these tumors is possible based on three factors that have been repeatedly observed to be important in treatment:

1. Size of the uterus. This is a fair index of tumor growth, for this tumor tends to grow locally for long periods of time with or without extension or metastasis, and size may serve as a clinical clue to its advancement and even local extension, though an imperfect one.

This factor may be estimated on bimanual examination or by depth of uterine sounding at diagnostic curettage if fibroids complicate the external evaluation.

2. Involvement of the isthmus or cervix. This important consideration will indicate the need for treatment of lower parametrial lymphatic channels and primary pelvic lymph nodes. It may be diagnosed usually on fractional curettage, although some prefer a hysterosogram.

3. Lack of tumor differentiation. This is another index to deep myometrial penetration and possible node involvement that serves as a warning that more aggressive treatment is required. Frozen section at curettage can offer such data in spite of its deficiency for more subtle histologic description. There would appear to be no more rational prohibition to the use of this important criterion for clinical staging than there is for the exclusion of other laboratory data, including hematologically and radiographically established ones, to obtain clinical information. There is little benefit to be gained

Table I. Pathology grading and result

Grade	No. of patients	Gross cure (%)
I	204	62.3
II	85	52.9
III	65	32.3

Table II. Involvement of the cervix

Treatment	No. of patients	Gross cure (%)
Radiation only	8	12.5
Surgery	8	12.5
Preoperative radium and surgery	7	57.1
Total	23	26.1

Table III. Depth of uterine invasion and result

	No. of patients	% of cases	Gross cure (%)
Endometrium only	38	13.0	86.8
Superficial myometrial invasion	108	36.9	72.2
Deep myometrial invasion	87	29.7	37.9

Table IV. Adnexal involvement

	No. of patients	Gross cure (%)
Tube	14	92.9
Ovary	50	28.0

Table V. Grade and myometrial invasion

Grade	No. of patients	Local disease (%)	Deep myometrial invasion (%)
I	160	56.8	20.6
II	79	49.3	34.1
III	58	25.8	53.4

Table VI. Result by stage

Stage	No. of patients	Gross cure (%)	Net cure (%)
I	86	69.8	85.7
II	124	58.9	76.8
III	46	45.7	56.8
IV	0	0	0

from the gloomy prognosis if the data supporting it cannot be used for constructive therapeutic action. Opening the specimen in the operating room after it has been removed by simple total hysterectomy for appraisal of myometrial extension is a more direct method but it comes after the opportunity for preoperative radium treatment has been sacrificed and the parametrial lymphatic channels cut through. One may still deal with the nodes surgically or radiotherapeutically thereafter to be sure.

It is of interest to note here the correlation between anaplastic tumors and deep myometrial penetration in our series (Table V).

A clinical corpus staging (*advance one stage for anaplastic tumor and/or involvement of the cervix*) may then be made using these factors:

Stage I. Uterus normal in size. The cervix is uninvolved and the tumor differentiated.

Stage II. Uterus is mildly enlarged, up to size of 2½ months' pregnancy or 10 cm. in depth.

Stage III. Uterus markedly enlarged; over size of 3 months' pregnancy or more than 10 cm. in depth.

Stage IV. Bladder or bowel involved. Distant metastases.

Table VI shows the application of this staging to a group of our patients and the decline in cure rate with advancement in stage. Our results by treatment modality will be presented below, and the correlation of treatment with stage of clinical advancement will be presented thereafter.

Contribution of radiation

The combined therapeutic technique of preoperative radium followed by abdominal hysterectomy has gained widespread favor in American clinics for the treatment of endometrial cancer.²⁻⁶ The advantages claimed for this preparation for operation by radium include: (1) devitalization of the tumor surface to increase the efficiency of later surgical treatment by preventing spill and implantation metastases; (2) diminution in uterine size to facilitate operation; (3) fibrosing of

the uterus to seal lymphatics and prevent uterine rupture during operation; and (4) improvement in cure rate by the addition of preoperative radium in individual clinics.

The packing method of radium distribution in the corpus (after the Stockholm method) is to be preferred to the use of a tandem. The tandem is theoretically inefficient in enlarged uteri and its use preoperatively adds nothing to later hysterectomy in a uterus of normal size with a localized, well-differentiated tumor. If the packing method is used, vaginal fornix sources should also be placed, for one major area of extension is the vaginal vault.

During the study period which we are reporting, the therapeutic preference in our clinic has been for preoperative radium placement by a dispersal or packing technique, followed by abdominal hysterectomy in 4 to 6 weeks. We have allowed the radium to remain in position for a total dosage of 4,000 to 6,000 mg. hr. in one sitting, if applied as a preoperative measure. It will be noted from Table VII that we have been content on occasion with surgical treatment only.

In our general series of patients we have attained a superior result with the combined mode of therapy over that with operation only. It may be of further interest to note that the application of a clinical staging such as outlined above permits an analysis that suggests the area of selection that may prevent a demonstration of superiority of the combined mode of therapy in some other series (Table VIII). We can only conclude from our study that a uterus of normal size with a well-differentiated local lesion will be treated equally well by surgical treatment only, whereas proper radium patterns followed by surgical treatment offer a more efficient method for the more commonly encountered mildly to moderately enlarged uterus and even expand the scope of the treatment in those patients with the cervix involved or with anaplastic tumor.

We have studied the histologic radium response of these lesions and observed an increase in the cure rate proportionate to the

Table VII. Treatment

Treatment	No. of patients	Living and well 5 years	Gross cure (%)	Lost to follow-up or died of intercurrent disease*	Net cure (%)
Radiation	69	13	18.8	23	28.3
Surgery	121	66	54.6	21	66.0
Preoperative radium and surgery	170	116	68.2	28	81.7
Total	360		54.2		67.7

*Forty-six patients (12.7 per cent) were lost to follow-up; 26 patients (5.65 per cent) died of intercurrent disease; 5 patients had radical hysterectomy.

Table VIII. Result by stage*

Stage	No. of patients		Gross cure (%)		Net cure (%)	
	Surgery	Combined	Surgery	Combined	Surgery	Combined
I	29	57	72.4	68.4	80.8	88.6
II	51	73	47.1	67.1	70.6	80.3
III	26	20	38.5	55.0	50.0	64.7
IV	0	0	0	0	0	0

*Two hundred fifty-six cases of series classified; 2 Stage IV cases treated with radiation only; combined indicates preoperative radium and surgery.

efficiency of the radiation in the excised uterus (Table IX). We have also observed an apparent diminution in the local recurrence rate with the combined mode (Table X).

A brief recapitulation of the results obtained by others is presented in Table XI to allow a gross comparison of surgical and combined treatment in those clinics reporting a more or less comparable surgical era.⁷⁻³⁰ This crude attempt to remove factors of selection in individual small groups by obtaining a mean cure rate once again gives the advantage to the combined therapy.

We have reserved postoperative x-ray therapy for those patients in whom surgical treatment revealed cancer spread beyond the uterus. Such an advanced group is, of course, selected unfavorably and permits no conclusions concerning the place of this modality of treatment in the majority of more favorable cases.

Contribution of surgery

Total abdominal hysterectomy has been found to be an efficient and safe procedure for the treatment of corpus cancer. When

combined with radium implantation it has usually been performed 4 to 6 weeks following the placement of the radium, although in recent years there have been studies suggesting that earlier operation offers no increased technical hazard. Whether or not this earlier timing of operation confers as much radiotherapeutic benefit as does the later one has not been established as yet. The commonly utilized surgical procedure and the one which has been most popular in our clinic is total abdominal hysterectomy performed by the extrafascial technique with a wide

Table IX. Radium response and result

	No. of patients	Gross cure (%)
No response	22	50.0
Moderate response	95	70.5
No cancer seen	51	74.5

Table X. Local recurrence

	Vagina	Wound
Surgery	9	2
Preoperative radium and surgery	2	0

Table XI. Results

Author	Hysterectomy		Radium and hysterectomy		Radium pattern
	No.	Cure rate (%)	No.	Cure rate (%)	
Masson	306	66.6			
Bastiaanse	250	66.9			
McKelvey	94	73.0	95	74.0	
Marshall	31	90.0	48	88.0	Tandem
Payne	46	80.4	28	92.9	Tandem
Miller and Henderson	20	53.3	16	86.6	
Speert and Peightal	95	48.0	39	54.0	Tandem
Palmer			30	80.0	
Waterman			67	61.0	Tandem
Corscaden	62	54.0	127	68.5	Tandem dispersal
Webb, Margolis, and Traut	43	65.0	49	71.0	
Scheffey	16	62.5	46	91.3	
Cosbie	68	63.2	47	70.2	
Randall	30	60.0	98	81.6	Packing
Ingersoll and Meigs	124	58.8	89	65.2	
Sandberg and McLennan	39	92.3	22	90.9	Tandem, Y or Δ
Schmitz			26	65.4	Y applicator
Kamperman	14	57.1	29	86.1	
Sherman and Arneson	57	70.0	91	72.5	Tandem or packing
Taylor and Becker	17	64.7	31	64.5	Tandem
Leucutia	71	47.4	64	81.2	
Hundley			32	84.0	
Brindley			24	79.0	
Kottmeier			48	72.0	
Total	1,383	64.0	1,146	76.5	

vaginal cuff, and bilateral salpingo-oophorectomy.

In an era when chemical, antibiotic, and anesthesiologic advances have permitted increasing surgical latitude, it has become necessary to defend the use of simple hysterectomy for corpus cancer when other tumors have become the object of more radical surgical treatment. It has been suggested that the lymph nodes and parametrial channels are proper areas for surgical dissection in this disease and that one might increase the cure rate by utilizing surgery. Some groups have undertaken the policy of routine radical hysterectomy for endometrial cancer. We have no data to bear upon this question but several considerations have dissuaded us from such a course of action:

1. Patients with corpus cancer are frequently elderly subjects, commonly obese, and occasionally circulatorily deficient; the morbidity and mortality of radical surgical

procedures will inevitably be high in this group unless selection is careful.

2. Although a positive node incidence of 20 to 30 per cent has been presented in some recent reports of corpus cancer,³¹⁻³⁵ these series are incomplete without specific reference to those patients who already have cervical or parametrial involvement.

3. Routine radical hysterectomy has not as yet demonstrated an improvement in over-all cure rate for unselected patients.^{31, 36-39}

4. The parametrium should not be a conventional channel of spread; it is probable that only deep involvement of the myometrium, isthmus, or cervix would make its dissection therapeutic.

It would seem, then, that radical hysterectomy could be added to the choice of treatment for corpus cancer with benefit if it is selected for those of operable status who have a great probability of deep myometrial invasion or involvement of isthmus or cervix.

For such patients the risk of more radical operations might be justified in order to gain surgical removal of nodes and parametrium.

Conclusions

One might then formulate a set of principles for treatment of corpus cancer based on our present knowledge of this disease in the following way:

Stage I. A minimal lesion well-differentiated and local with a small uterus offers a situation in which total hysterectomy alone gives as good a result as a combined technique.

Stage II. The moderate lesion with the uterus up to the size of a 2½ months' pregnancy (or smaller with an undifferentiated tumor) will be benefited by preoperative radium application by the Stockholm method or a modification thereof, followed by extra-fascial total hysterectomy. *It is important to note that the majority of corpus cancers fall into this group.*

Stage III. The advanced lesion with a large uterus (or one of moderate size with an undifferentiated tumor) and/or cervical, vaginal, or parametrial involvement may present a choice of treatments according to the suitability of the patient as a surgical candidate and technical considerations: (A) radical hysterectomy; (B) preoperative radium by corpus and cervix configuration followed by extended total hysterectomy and node dissection; or (C) preoperative x-ray therapy and total hysterectomy.

Stage IV. In this group of patients with involvement of the bowel or bladder, or distant metastases, it might be possible to salvage an occasional patient with involvement of contiguous organs by total pelvic exenteration. Treatment in this group must be individualized.

All stages. Postoperative x-ray treatment may be given patients with involvement of the cervix, parametrium, or ovary, with deep myometrial penetration of the tumor or overt pelvic node disease.

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Adequate anterior colporrhaphy

A new surgical approach for the relief of stress incontinence in women

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STRESS incontinence is due to a levator asthenia or a support problem and not a sphincter weakness, *per se*, as has been the traditional contention. It is directly allied to the normal processes of micturition and is manifested by a partial loss of the posterior vesicourethral angle. The weakness is a result of a diastasis of the pubococcygeal and puborectalis musculofascial elements of the levator ani at the bladder neck with herniation of the posterior cystourethral junction. This, in fact, allows a partial detrusion and thereby compromises the force of extrinsic resistance to the bladder floor segment. Thus, urine is involuntarily lost even with minor fluctuations of the intracystic pressure. This occurs in intermittent dribbles associated with factors that effect sudden, sharp rises in the intra-abdominal pressure, which in turn is reflected through the normal bladder mechanism with urine loss.

The concept of a weakened sphincter mechanism alone adequately explains only an overflow type of urinary incontinence. Thus, the detrusor concept becomes essential. The word "detrusor" was first used in relation to a supposed longitudinal muscle in the trigonal urethral axis and probably is an artefact due to postmortem changes. At present the detrusor connotation is related to a complete longitudinal muscle layer of the entire bladder wall.¹⁷ Detrusion is derived from the Latin verb, *detrudere*, to thrust

downward, and we have considered it entirely in relationship to the bladder neck. It is difficult to concede that this muscle layer, detrusor urinae, can have any effect other than as an integrated part of the elastic bladder wall contributing to the intracystic, hydraulic pressure. However, this concept does not deny that this muscle layer, under motor, neuronal influence imparts an additional thrust during the deflational phase of bladder function.

Second, "the muscle of micturition"¹¹ concept, although an anatomic miscue,²¹ attempted to explain a physiologic necessity. The sphincter mechanism must be forced open by unequal stresses to effect normal emptying. A mere lessening of tension, alone, within the sphincter itself, provides no acceptable explanation for stress incontinence, and stress incontinence is the only type of vesical function incontinence with a prospect of satisfactory and consistent solution in a surgical approach. The fact that stress incontinence has and can be cured by operative procedures (sling operations, etc.) not involving the sphincter mechanism directly is adequate proof of this point.

Certain expressed theories concerning etiology of stress incontinence are of interest. Jeffcoate and Roberts^{7, 8, 23} have emphasized the importance of the posterior vesicourethral angle; Kennedy¹⁰ has pointed out the necessity of urethral mobilization in natural micturition but still feels that stress incontinence is a manifestation of sphincter weakness and has described an operation designed to correct a sphincter defect.^{11, 12}

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From his descriptions and illustrations it appears that he also establishes a posterior vesicourethral angle together with mobilization of the urethra. In fact, then, is this actual re-enforcement of the sphincter or merely a rendering of the proper environment for its functional efficiency?

Although Hodgkinson⁵ takes full cognizance of the posterior vesicourethral angle, he also makes an emphatic point regarding the anterior or posterior rotation of the bladder. He states that, when the bladder is anterorotated, the urethral orifice is placed at the direct base of the bladder where the "hydrostatic" (his word) pressure is greatest; thus, urine is lost on stress. He then illustrates how repair rotates the bladder posteriorly and elevates the internal urethral orifice above the bladder floor, "carrying it away from the point of greatest hydrostatic pressure." At the same time, the posterior vesicourethral angle is missing in the first instance and established with the repair. It is difficult to comprehend how hydraulic (hydrostatic is not the proper

word) pressure with increased tension is greater in one part of the bladder than in any other. In the upright position, with the bladder inert, there may be some slight increase in pressure on a hydrostatic basis at the bladder base as compared with its fundus, but in this situation there is no urine loss. This occurs only with sharp increases in the intra-abdominal pressure which increments the hydraulic pressure within the bladder and equally in all directions if the sphincter remains closed. It seems unlikely that hydrodynamics play a specific part in stress incontinence other than as a force of detrusor and expulsion as with normal urination.

Kegel⁹ is one of the few American gynecologic investigators, along with Muellner,¹⁰ who have mentioned the pubococcygeus muscles and their fasciae as support structures to the bladder. Read²² believes that Kegel exercises (perineal) are excellent for minimal degrees of stress incontinence and are a definite benefit as a part of the postpartum routine. On the other hand, perineal gymnastics will not overcome a fully developed stress incontinence if the levator diastasis is of any amplitude. Although these muscular structures can be strengthened and thickened by exercise, this does not put substance back in the midline, and some such support is essential to sustain the posterior vesicourethral angle in denial of unwanted destruction. One must also remember that the urethra is commonly injured in childbirth but that the injury goes unrecognized. This is due to subsequent scarring, fixation, and urethral shortening. Exercise can do little to correct this condition and its contribution to the symptom of stress incontinence.

Practically all surgical repair procedures performed now and in the past to correct stress do tend, in some respect, to re-establish a posterior vesicourethral angle, although this is not always the primary intent. Plication of the so-called pubovesical fascia at the bladder neck (Kelly stitch) does have the effect of allowing the levators closer approximation to the midline. The fascial

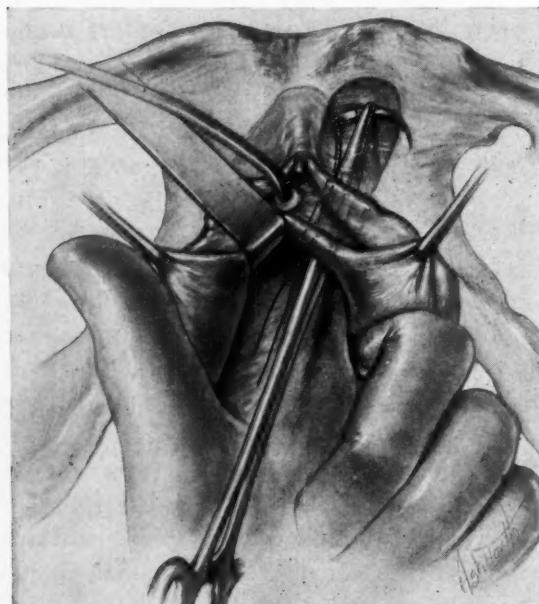


Fig. 1. Placement of the periosteal stitch after the paraurethral dissection into the retropubic space. It is placed at about the medial angle of the obturator foramen on the posterior surface of the pubic bone.

sling procedures interpose a high, false floor beneath the posterior cystourethral junction and re-enforce the posterior vesicourethral angle and do, thereby, correct stress incontinence if the sling maintains the proper tension. This would seem, however, to be unphysiologic because of a rigidity that would not have the resilience or functional facility of a properly supporting musculofascial shelf. The same complaint obtains with the interposition of other structures beneath the bladder neck, such as the uterus, bulbocavernosus muscles,¹⁵ ischiocavernosus muscles,⁴ round ligaments,²⁵ etc. The fixation must be high, should be resilient, and, ideally, should be a part of the initial operative approach.

The anterior vesicourethral suspension of Marshall, Marchetti, and Krantz is perhaps, at the present time, the most popular approach for previous operative failures or initially in cases wherein pelvic relaxation or prolapse is not a major factor. Here, the fixation is high with the submucosal connective tissue of the vagina (the same layer that Goff³ derided as a support structure) used to form a sling anchored to the periosteum of the pubis. This operation is appealing because of its technical simplicity and its high degree of success in the alleviation of stress incontinence. However, it is difficult to combine with an initial procedure from below wherein the "pubovesical fascia" is divided in the midline during the repair of the anterior vaginal wall. Also, this operation makes no allowance for mobilization of the bladder neck and urethra. If the so-called pubocervical vesicle fascia is of such poor support quality as some maintain,³ a measure of the success of the Marshall-Marchetti-Krantz procedure must be accredited to the levator muscles as they are allowed to reapproximate toward the midline.

It would seem, on the basis of the foregoing, that the anatomic approach to the problem of stress incontinence must deal in some way with the substance of the levators (pubococcygei) and their realignment beneath the bladder neck. Pacey²⁰ in 1949 described such an operation in which the pu-

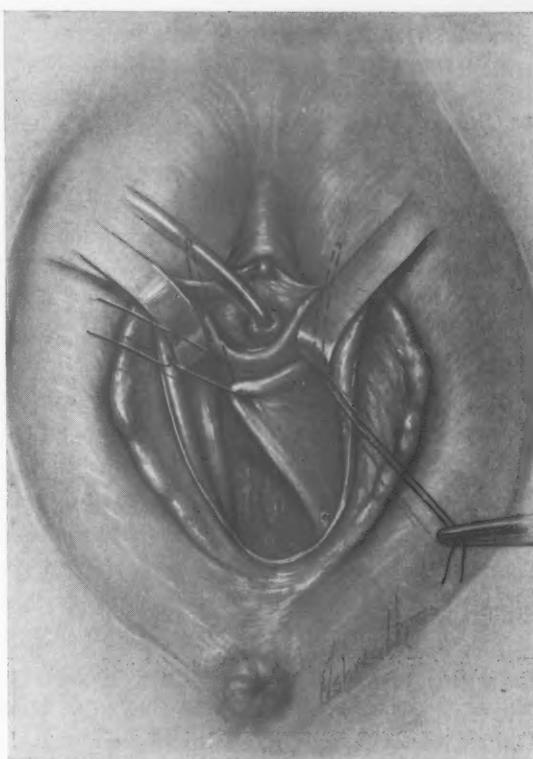


Fig. 2. Carriage at the left pubococcygeal muscle and fascia at the level of the bladder neck to the point of periosteal fixation on the contralateral side.

bococcygeal muscles were fixed together in the midline in support of the posterior vesicourethral angle. This method has been used extensively by Read,²² who points out, however, that the method is inadequate in many cases of stress incontinence because the fixation is not high enough behind the symphysis. Some surgical means from below with use of the musculofascial structures of the pubococcygeal and puborectalis portions of the levator ani muscles beneath the bladder neck with high fixation would seem to afford an ideal anatomic and physiologic basis for an improved anterior colporrhaphy, directed primarily at the relief of stress incontinence of urine.

The anterior wall as a part of the primary vaginal plastic operation has been greatly slighted. This portion of the repair is inseparable from the bladder function. It is stated that from 10 to 20 per cent of repairs of the anterior wall fail to correct,

result in, or allow the development of stress incontinence at a later date.^{2, 24} A number of techniques have been developed and advocated to correct these anterior failures, such as muscle and fascial sling operations,^{1, 4, 13, 16, 18, 22} "pin-up" procedures,^{9, 14, 15} and interpositions of other structures.^{6, 15, 25} The rectocele and the enterocele and their associated malfunctions have been substantially solved by improving the initial operation. Would it not seem that an improved primary anterior repair might also solve urethrocytic difficulties with the *initial attempt*? Also, would it not be better to perform the repair *initially* in all of these patients as if the symptom of stress incontinence always exists in order to obviate the hazard of stress potentiality? The purpose here is to suggest a surgical procedure in accordance with the above-stated rationale.

Operative technique

The technique about to be described produces a well-supported anterior vaginal wall. In addition, it reconstitutes the posterior vesicourethral angle and allows for mobilization of the bladder neck and urethra. These are the essential necessities of an adequate anterior colporrhaphy.

The repair is started in the usual fashion with undercutting of the mucosa and blunt dissection of the bladder and its connective tissue well out into the lateral angles. A No. 16, 5 c.c., Foley bag catheter is placed in the bladder and the bag inflated. Blunt dissection is carried upward with the index finger on either side of the urethra well into the retropubic space. An area is cleaned of all connective tissue overlying the periosteum on the inside superior aspect of the pubic bone; again, this must be done bluntly because sharp dissection in this area may start bleeding from the retropubic venous plexus. The dissection penetrates the urogenital diaphragm lateral to the urethra. This is of little consequence, however, because the structure has little function other than as a distal moorage for the urethra. It is still intact superiorly. Thus, the vesicourethral



Fig. 3. Carriage of the right pubococcygeus muscle and fascia in a like manner overlapping the left. This recreates a pelvic floor shelf beneath the posterior vesicourethral junction. The mobilized bladder floor is carried upward and reangulated in a normal fashion with the urethra. The urethra, itself, is elongated.

junction and the urethra become essentially free except for the superior and distal attachments to the pubovesical ligaments and the urogenital diaphragm, respectively.

The patient is then tipped into a moderately deep Trendelenburg position which, with the help of a small right angle retractor, improves the visualization of the retropubic area. No. 2-0 chromic catgut on a small, sturdy (No. 4) trocar needle is used to place a suture through the periosteum fairly high on the posterior surface of the pubic bone (Fig. 1). This is approximately at the level of the medial angle of the obturator foramen, which can be palpated with ease. This is done on either side while the bladder and urethra are protected by retraction to the opposite side. (The suture should be looped or swaged into the needle to implement its recovery in case contact is

lost with the holding instruments.) The relative position of this stitch will vary somewhat from patient to patient; the wider the pubic arch the more nearly the position must approach the midline. The suture is properly engaged into the periosteum when there is no give on traction. The placement of the suture constitutes the most important part of the procedure. In certain individuals, because of anatomical variations, it may have to be done blindly by palpation with use of two needle holders, one to insert and one to extract the needle. With a little patience and practice this can afford no great obstacle.

The bladder neck is located by palpating the position of the Foley bag within the vesical lumen (Fig. 5). Very light traction should be used on the catheter; otherwise, in a well-relaxed bladder floor the neck may be assumed to be too far distal because of

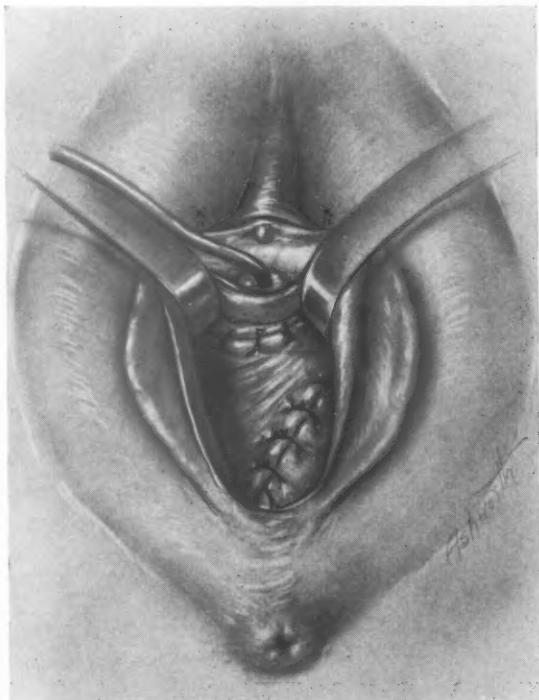


Fig. 4. Placement of sutures re-enforcing the imbrication of the pubococcygeal muscles. These would maintain pubococcygeal juxtaposition even if the periosteal end of the fixation failed. However, the high fixation is still dependent upon the integrity of the periosteal sutures.

funneling of the trigone. Laterally, at the level of the bladder neck, are the usually well-developed, shiny fibers of the pubococcygeus and puborectalis fascia of the levator ani muscle. These are quite definite and run in an anteroposterior direction and are much more discernible at the level of the bladder neck than toward the vaginal apex, for, as they are traced posteriorly, they disappear around the lateral vaginal walls at the vaginal apex. The more marked the relaxation, the wider the levator diastasis and the further lateral will lie these fascial structures. The sutures placed previously in the pubic periosteum are now threaded on a small round point needle and carried through a good-sized bite of the above-described fascia at the level of the bladder neck on the contralateral side (Fig. 2). One must be careful to place one side slightly above the other so that when the knots are made snug the pubococcygeal muscles are directed upward and to the opposite side, neatlylapping one over the other (Fig. 3). This imbrication closes the diastasis at the bladder neck just as the fascia is overlapped in a ventral hernia repair. This does not twist or distort the bladder neck in any way because these fascial structures slide over the deeper elements much like the hide at the scruff of a dog's neck. This lifts the vesical neck and angulates it with the urethra which is pulled taut behind the symphysis and is, thereby, elongated. In other words, this recreates the subpubic groove which is the hallmark of a properly supported and aligned vesicourethral complex. It does not and cannot constrict the urethra if, in fact, the periosteal stitches are away from the midline and the imbrication is carried from the level of the bladder neck. There is nothing over the superior arc of the urethra to constrict it. Thus, the shelf of the anterior pelvic diaphragm is re-established.

In actual practice, we grasp the pubococcygeus with an Allis clamp at the level of the bladder neck and carry it to the point of the periosteal fixation in order to test the tension to be placed upon the anchoring su-

ture. If this be too great, the dissection is carried farther posterior in an attempt to increase the mobility of the pubococcygeus fascia. The side with the least mobility is fixed first, and the side with the most is lapped over it. If a reasonable tension cannot be adjusted, the periosteopubococcygeal imbrication should be abandoned in favor of the Pacey procedure²⁰ in which these musculofascial structures are approximated in the midline beneath the bladder neck.

This procedure at this point will have almost completely obliterated the cystocele. However, we feel that it would be injudicious to rely upon these two sutures alone, and we insure the repair by suturing one pubococcygeus to the other to re-enforce their juxtaposition high beneath the bladder neck (Fig. 4).

The remainder of the colporrhaphy is traditionally completed. One should not at-

tempt to place sutures distal to the vesical neck about the urethra because this may defeat the purpose in two ways: (1) by foreshortening the urethra and/or (2) by causing more reaction about the urethra with subsequent scarring and fixation.

After being trimmed, the vaginal mucosa is approximated and fixed down to the underlying repair from the bladder neck to the vaginal apex, but again not along the urethra. This part of the repair is also more easily accomplished with the patient remaining in the Trendelenburg position because, if the repair is proper, one is working fairly high behind the symphysis (Fig. 6).

Cases and complications

During the past 9 years 67 of these anterior repairs have been performed, 57 of which were on either my own patients or

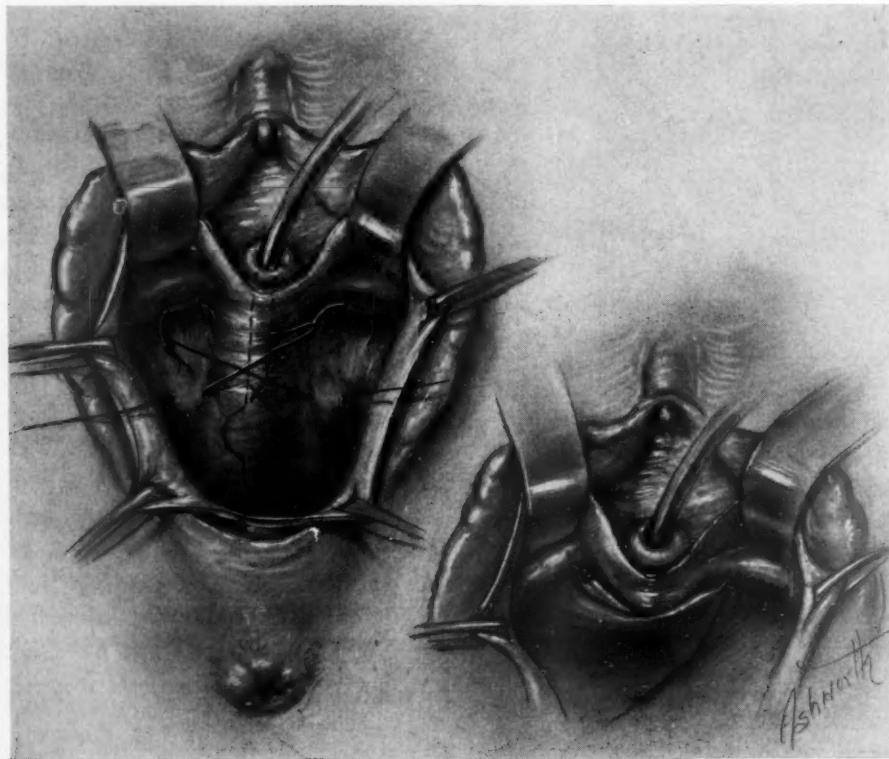


Fig. 5. This is a composite illustration demonstrating the location of the bladder neck (X) and its relationship to those portions of the pubococcygeal muscles that are to be carried into apposition with the periosteum. The periosteal stitch, however, is much higher than this illustration would tend to indicate.

those of my partner, Dr. James M. Whately. The remainder were done in consultation with referring surgeons. All of these repairs with the exception of the last 11 were done 2 or more years ago.

To date there have been 3 failures, 2 of which can be excluded from the repair itself. One was the first repair performed in 1949, before the deleterious, foreshortening effect of paraurethral sutures was understood. The other was another gynecologist's patient who proved later to have a neurogenic bladder on the basis of a spinal cord tumor. In the third case the periosteal sutures evidently gave way, for there was a recurrence of the cystocele to a partial degree but, to date, no recurrence of stress incontinence. Uncorrected, this would be a failure rate of 4.5 per cent. If the first 2 failures are eliminated because of the stated extenuating circumstances and if it is assumed that the third failure will eventually result in recurring stress incontinence, a fair failure estimate for this group of cases could be stated to be 1.5 per cent on a corrected basis.

The average age of this group was 46.7 years, the eldest 73, the youngest 31. Forty-nine of the 67 had definite stress incontinence; one had neurogenic incontinence. Seventeen operations were performed in the absence of the symptom of stress on a basis of philosophic speculation as to when the procedure is indicated. We now incline to the prospect that the indications should include any case wherein the relaxed pelvic floor is symptomatic and the subpubic vaginal groove (the posterior vesicourethral angle) has been destroyed.

Ideally, childbearing should be at an end before the repair is contemplated. Otherwise, if the symptoms are present and distressing, age alone should not be a deterring factor. Fourteen operations were performed as a part of the so-called combined procedure in which the uterus was removed abdominally for other reasons after the vaginal plastic. Four were carried out as a part of a vaginal plastic operation without hysterectomy. One was done in association with a

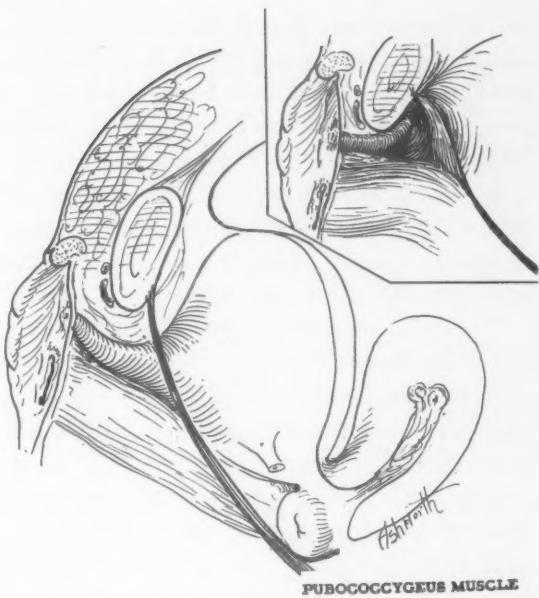


Fig. 6. This figure illustrates the sagittal relationships of the repair. The depth behind the symphysis is much greater than can be illustrated from a perineal view. This also emphasizes how the repair in its lifting of the bladder floor elongates the urethra rather than foreshortening it.

Manchester procedure, and 48 were associated with vaginal hysterectomy.

The complications encountered during the operative time were few. There were 3 cases of excessive bleeding from the retropubic dissection. All occurred before it came to mind that sharp dissection in this area is contraindicated. All of these were handled easily by the use of an Oxycel pack and were unassociated with postoperative sequelae from this cause. In one case, a broken needle in the retropubic area caused consternation but, fortunately, it was found. One cannot take this periosteal stitch without a heavy-gauge, small-curved trocar needle. The operative time consumption is mainly taken with the proper placement and alignment of these periosteopubococcygeal sutures. At times they tear out or break when pulled up under too much tension. It then becomes necessary to replace the periosteal end more toward the midline or perhaps to take a more substantial bite in the pubococcygeus more at right angles to its fibers.

We have used No. 2 chromic catgut suture for the periosteal stitch because of its strength. No. 2 silk has been tried, but it was found that in too many cases a granulomatous fistula formed to the vaginal mucosa, and it became necessary to remove the suture at a later date. A nonabsorbable, non-reactive, strong, pliable suture material would be ideal for this purpose.

There have been no known cases of post-operative periostitis with these procedures. One patient complained of chronic aching in the pubic arch area, but nothing could be visualized on x-ray examination, and the symptom gradually disappeared over a period of months. We do not think that postoperative urinary retention presents a great problem; however, this is a factor that has wide variation from patient to patient. An indwelling catheter is used over a 5 to 6 day period. All but 10 of the patients were discharged within 12 days and were urinating with a residual under 100 c.c. These 10 were sent home with a catheter in the bladder. Only 2 went longer than 6 weeks without the ability to urinate spontaneously. Long-standing urinary residue of over 100 c.c. was a complication in 3 cases. This is best handled by continuous bladder drainage with a large 20 or 22 Foley catheter with a plastic leg urinal during the day and a bedside bottle at night. Bladder tone and adequate emptying have not failed to return with this care.

Prolonged urinary urge after this procedure is seen occasionally just as it is after the Marshall-Marchetti-Krantz operation. This is usually mitigated by time, 8 to 10 weeks as a rule.

Comment

In the case of records, this repair has been placed under the reference, "periosteal urethroplasty"; it might better be called a periosteopubococcygeal imbrication. We feel that it accomplishes everything the Marshall-Marchetti-Krantz procedure does, but in a one stage initial operation from below done simultaneously with the original vaginal plastic operation. It is felt that it strengthens the midline even more than the "pin-up"

repair, because of the overlap or imbrication feature. Fascial imbrication is a time-honored technique for herniorrhaphy, and cystocele is in effect a hernia of the bladder and vesical neck due to a diastasis of the anterior aspect of the levator ani muscles.

Case follow-up in private practice leaves something to be desired. During the first year or so the patients return on a fairly regular basis, but thereafter re-examinations are quite sporadic. Fifty-five of the procedures in the total series were performed more than 2 years ago. Of this group we have had a complete follow-up on a 2 year basis only. However, it is felt that if the support is still good and the incontinence still cured at the end of 2 years the over-all result should continue to be good.

Conclusions

1. A new surgical technique in the performance of the anterior colporrhaphy is presented along with a review of 67 cases. There is a corrected failure rate of 1.5 per cent on the basis of a 2 year follow-up.

2. In order that the anterior colporrhaphy be adequate, it must accomplish the following: (A) give a well-supported anterior vaginal wall and (B) correct stress incontinence both actual and potential by: (1) re-establishment of the posterior vesicourethral angle and (2) mobilization of the urethra and bladder neck without shortening of the former.

3. The anterior vaginal wall has been neglected in our thinking as concerns the "initial repair" during vaginal plastic procedures.

4. The anatomy of the area has not been properly emphasized as it relates to the "adequate" anterior colporrhaphy. The role of the pubococcygeal and puborectalis portions of the levator ani muscles has been largely ignored.

5. The presurgical assessment must evaluate accurately any associated urinary incontinence as to its cause.

6. If a relaxed pelvic floor is symptomatic and a repair indicated, it is felt that the suggested technique should be performed

even without the stress incontinence. The anatomic relationships of the bladder and

urethra should be normalized in order to reduce the hazard of future stress potential.

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Keeping the patient with bladder fistula dry

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FROM the beginning of urine leakage from a vesicovaginal fistula until it can be stopped by surgical repair women suffering from this disorder are miserable. To date no mechanical or pad device has been entirely successful in keeping such women dry and safe from the disagreeable odor surrounding their persons. A 6 month period of time usually must elapse after a fistula occurs before the tissues involved are sufficiently vascular for successful repair. In this waiting interval relief from constant drainage of urine would be welcomed by the patient and her doctor.

Recently, an internal menstrual cup manufactured by Tassette, Inc., Stamford, Connecticut was described for use by women during menstruation in place of perineal pads or tampons.¹ The cup, made of soft, pliable rubber, has a double rim which is thickened and rounded so as to engage the vaginal musculature and secure its position after insertion into the vagina (Fig. 1). It is 2 inches deep and 1 3/4 inches in diameter and has a slender, hollow removal tip which is retained within the labia when in use. The device when folded is easily inserted, fits any vagina (except one that is prolapsed), and makes it virtually leak-proof. After insertion a slight forward pull of the stem creates a semi-vacuum in the upper vagina.

The dome of this cup was perforated through the hollow stem with a red-hot wire, and a No. 12 French catheter was fitted snugly over the stem. This, with a strap-on-leg type rubber urinal, was given to a patient with a vesicovaginal fistula following hysterectomy, and she now stays completely dry and free from uriniferous odor.

From the Woman's Clinic.

The patient, para iv, suffered shock with rupture of the uterus and rupture of the bladder after 48 hours of labor complicated by a hydrocephalic infant and several attempts at delivery with high forceps. A total



Fig. 1. Illustration of the Tassette cup in place in the vagina.

hysterectomy and repair of the bladder were carried out, but a midline vesicovaginal fistula resulted. She is awaiting surgical repair of the fistula.

Addendum. Since this article was submitted for publication the fistula has been successfully repaired.

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CURRENT OPINION

Re-evaluation

The maternal-fetal barrier

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THE maternal-fetal barrier has been given considerable attention in recent years. For clarification, however, it is important to stress that the term "placental barrier" is no longer considered inclusive enough to represent the total maternal-fetal relationship involved in pregnancy. The amnion, membranous chorion, and decidua vera deserve consideration as well as the villus placenta and decidua basalis. It is the passage of large protein molecules or substances across this barrier to which this discussion will be directed. Of course, some of the protein substances with which we are concerned do not cross the barrier but are part of the barrier prior to being introduced into either the fetal or maternal circulation. Since the recognition by Levine and associates¹⁵ in 1941 of the role of the Rh(D) factor in the etiology of erythroblastosis, the passage of rather large substances such as agglutinogens and agglutinins or even erythrocytes has been presumed to be possible. There has been considerable effort to determine the mechanisms of such transfer. Despite the reported

findings, very little of the information gained has been applied—from a preventive medicine standpoint—to everyday obstetrics. All interest has been concentrated on the cases already demonstrating blood incompatibility problems. This discussion will not be limited to the transfer of blood agglutinogens only but will also include the transfer of thromboplastin substances presumed to be involved in hypofibrinogenemia as noted, for example, in amniotic fluid infusion.

Survey of problem

Most of the speculation as to the method of transfer of protein molecules across the maternal-fetal barrier occurred soon after the role of the Rh(D) factor in erythroblastosis was proved. It is interesting to review the suggestions of the various workers. Levine¹⁴ in 1944 suggested that the constant leaking of fetal erythrocytes across the placenta during the course of pregnancy might account for the increases in Rh(D) antibody titers. Wiener²⁸ believed that the chorionic villus is impermeable during pregnancy but that fetal erythrocyte transfer occurs by rupture of chorionic villi during labor and at the time of delivery. According to Potter,²³ greater rises in Rh antibody titers occur as a result of delivery than during the entire

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pregnancy. Further proof of transfer of agglutinogens can be demonstrated by observing the rise in major blood group antibody titers that are shown in most ABO heterospecific pregnancies. Such a pregnancy is one in which the infant's blood contains A or B antigens and the mother's does not. Approximately 25 per cent of all pregnancies⁶ in the white population in this country are ABO heterospecific. In these heterospecific pregnancies, a slight rise in the specific antibody titer involved occurs in early pregnancy,³ then the level remains relatively stable until delivery, following which a marked rise occurs. Although eventually, the serum does show some decrease in the titer, it always remains at a somewhat higher level than was noted prior to pregnancy. Regardless of the mechanisms, there is little doubt that transfer of protein substances across the maternal-fetal barrier does occur. In all likelihood, it is by one of the following suggested mechanisms: (1) diffusion, (2) cellular transfer of material, (3) transfer of intact particles by pinocytosis, and (4) pathologic leaks.

Rucknagel and Chernoff²⁴ studied the levels of fetal type hemoglobin in the maternal circulation during pregnancy in an effort to demonstrate whether any leakage of fetal blood does occur. Complicating this study, however, is the fact that an adult does produce a certain amount of fetal type hemoglobin and that the amount produced may be influenced by such things as a high gonadotrophic hormone level. Nevertheless, high levels of fetal type hemoglobin are noted in the maternal circulation in early pregnancy with a gradual drop toward term. In addition, the rate of decrease of fetal type hemoglobin in the second half of pregnancy is consistent with what would occur if the normal rate of blood destruction occurred and if no new erythrocytes with fetal type hemoglobin are produced or enter the maternal circulation after the fifth month. This may explain why, in ABO heterospecific pregnancy, the anti-A or anti-B titer goes up in early pregnancy but then remains rather constant until delivery, at which point there is a precipitous rise in titer. There is usually

no corresponding rise in fetal type hemoglobin in the maternal circulation to account for the precipitous rise in antibody titers at the time of delivery and this would have to be explained by some other mechanism, such as amniotic fluid infusion, which will be discussed later in this paper. According to O'Connor and associates,¹⁹ when higher levels of fetal type hemoglobin are found in the mother immediately post partum, there is usually an associated fetal anemia.

Other studies done on the fetal type hemoglobin by Bromberg and co-workers⁴ have demonstrated high levels in the retroplacental clot found in cases of abruptio placentae and also in the normal clot found during the third stage of labor. This is considered to be good evidence that these clots are mixtures of both fetal and maternal blood. Very likely, any strong contraction between delivery of the baby and delivery of the placenta could force retroplacental blood into the maternal venous sinuses of the uterus. In fact, in cases of abruptio placentae, higher levels than usual of fetal type hemoglobin are noted in the maternal circulation.

Of course, the occurrence of emboli of chorionic villi in the lungs of women coming to autopsy is one of the strong arguments in favor of transfer of fetal tissue at the time of delivery. Therefore, it is not necessary to consider only the passage of erythrocytes when discussing the interchange of blood antigens since recent studies have demonstrated that the amniotic fluid, amnion, chorion, and even the decidua vera, which is maternal tissue, contain the antigens peculiar to the blood of the fetus when the fetus is a secretor even though the mother is of a different blood group. Eighty per cent of all babies are secretors. The incidence of amniotic fluid entering the maternal circulation may be more frequent than was previously considered. Stone and associates²⁶ believe that the occurrence of mild, possibly undetectable, amounts of amniotic fluid embolism may not be too uncommon. There is some certainty that some substance in the amniotic fluid can cause hypofibrinogenemia and, now that this fluid is known to contain

major blood group antigens,⁷ there is further reason why amniotic fluid infusion should be prevented.

The incidence of erythroblastosis is relatively low but, when it does occur, it is tragic. If the husband is homozygous, the outlook is poor. It would seem, therefore, that it would be more important to prevent the original sensitization than it would be to be concerned after sensitization does occur. All of the long-range effects of sensitization are not really known. Six to 14 per cent of stillbirths are due to erythroblastosis but 20 to 30 per cent of the stillbirths remain unexplained,¹⁵ and may be related to some type of blood incompatibility. Other conditions which have been reported to be somewhat affected by the ABO blood groups are toxemia, abortions, and fertility.²¹

The discussion about prevention of hypofibrinogenemia can very readily be considered with the prevention of sensitization to blood factors. In both situations, it is assumed that some substance enters the maternal circulation. In the case of hypofibrinogenemia, the effect is sudden and startling and easily associated with the underlying obstetrical complication such as abruptio placentae, dead fetus, etc. However, it can be stated with some certainty that mild degrees of hypofibrinogenemia go unnoticed with more than average blood loss in the immediate postpartum period but never at a rate to be alarming. As far as blood incompatibility is concerned, however, by the time the clinical syndrome presents itself, little is left to indicate what conditions in the previous pregnancy may have contributed to the sensitization that has occurred. The same complications that lead to hypofibrinogenemia (abruptio placentae and amniotic fluid infusion, for example) could also lead to sensitization to incompatible blood factors and, therefore, the prevention of these complications would be helpful in either case. The scope of the problem is at once obvious when one realizes that 35 per cent of all pregnancies have potential ABO incompatibility and over 15 per cent have potential Rh(D) incompatibility not to mention in-

compatibility due to the numerous other blood antigen systems.

Application of findings and recommendations

It is my opinion that certain obstetric procedures, if used regularly, may decrease the incidence and severity of problems arising as a result of the passage of protein substances across the maternal-fetal barrier and that some obstetric procedures regularly practiced may be increasing the incidence and severity of these problems.

Prenatal care. First and foremost in any discussion of ideal obstetrics is the emphasis on good prenatal care. It is not the purpose of this paper to list all the previously recommended procedures which constitute good prenatal care. Recently, however, the addition of the citrus bioflavonoids and high doses of vitamin C to the usual prenatal vitamin supplements has been recommended, particularly in patients with a history of erythroblastosis. They supposedly decrease capillary fragility and permeability and promote growth and healing. The high rate of decidual hemorrhage as a contributing factor in abortions has encouraged many physicians to add these substances to the therapy given to threatened and habitual aborters.^{10, 27} The bioflavonoids and ascorbic acid are innocuous and relatively inexpensive. If there is any objection to using the bioflavonoids in capsule or pill form, surely no one could object to a large glass of chilled orange juice daily throughout pregnancy. What better time could there be to administer a substance which might promote growth and decrease capillary fragility than in early pregnancy, during which time rapid implantation is occurring, a certain amount of instability exists, considerable interchange of fetal and maternal substances may be quite common, the maternal fibrinogen is at its lowest range,¹¹ and the maternal circulating fibrinolysins are at their highest point.² Jacobs⁹ has presented evidence of more successful results in cases of Rh isoimmunization when the mothers were maintained on high doses of ascorbic acid and the bioflavonoids

during the entire pregnancy. Perhaps the higher incidence in winter than in summer of toxemia, uterine bleeding, and other complications including abruptio placentae and rupture of the marginal sinus may be related to the decreased dietary intake of the bioflavonoids and ascorbic acid in the form of fruits which normally occurs in the winter. Pasamanick and Knobloch²⁰ found the incidence of the bleeding complications in January, February, and March to be almost double the incidence in July, August, and September, while there seemed to be no significant difference in the incidence of most other complications in the summer and winter months.

Significance and prevention of abruptio placentae. From previous discussion, it would seem that isoimmunization would be more likely to occur in the presence of abruptio placentae. With a mixture of fetal and maternal blood in the retroplacental clot and the probability that some of this retroplacental blood enters the maternal circulation with the accompanying tetanic uterine contractions, it would appear that this would be a complication to be particularly avoided in potential Rh(D) or ABO heterospecific pregnancy. Such a case was recently reported by Hartmann and McGanity.⁸ The patient was hospitalized during the early second trimester of pregnancy with a cerebrovascular accident. At this time, self-limiting hypofibrinogenemia was noted. Later, at term, an old retroplacental clot was found. The infant at birth exhibited what was thought to be a mild form of ABO incompatibility. The sequence of events could have been either of the following:

1. An amniotic fluid infusion which produced anaphylactic shock was interpreted as a cerebrovascular accident and resulted in hypofibrinogenemia. This hypofibrinogenemia predisposed in the production of the small occult abruptio placentae. Either the amniotic fluid infusion or the abruptio placentae could have resulted in isoimmunization.

2. The abruptio placentae caused hypofibrinogenemia which contributed to the cerebrovascular accident.

Abruptio placentae is severe enough in itself and ideally, if possible, it should be prevented. The added implication that hypofibrinogenemia and isoimmunization can occur in association with abruptio placentae would make prevention more imperative, especially in cases in which potential blood incompatibility exists. It is not my purpose to consider the usual factors of good prenatal care, toxemia, etc., and their relationship to this condition. The bioflavonoids have already been discussed. To my knowledge, very little has been written, however, about the incidence of abruptio placentae following the use of the broad-spectrum antibiotics. The resultant reduction of vitamin K-producing bacteria in the intestines following the administration of antibiotics produces some blood coagulation defects and this would predispose to abruptio placentae just as the administration of Dicumarol does. Some incompatibility of the bioflavonoid, rutin, and the sulfonamides has also been reported.¹³ Because of the fact that early and active treatment of infection in prenatal patients has been recommended, perhaps the antibiotics have been used too liberally just as they have in other fields of medicine. If the use of antibiotics is considered necessary, then an increase in dosage of vitamins, particularly vitamin K, should be considered.

Experimental evidence in the production of abruptio placentae in dogs by Nesbitt and co-workers¹⁷ would seem to incriminate elevated pelvic venous pressure as one possible factor in the pathogenesis of placental abruption. The counterpart in humans may very well be the "supine hypotensive syndrome" found to some degree in about 11 per cent of pregnant women. Smith and Fields²⁵ presented a case in which they felt that pressure of a flaccid uterus on the inferior vena cava caused a syncopal attack by blocking venous return thus increasing venous pressure, which resulted in abruptio placentae. There is greater pressure on the vena cava in twin pregnancy and the incidence of abruptio placentae in multiple pregnancy¹² is much higher than in single pregnancy. Montgomery¹⁶ has even gone so

far as to recommend delivery in the Sims position not only to relieve the pressure on the vena cava but also because the best oxygen saturation pattern of the newborn is noted in this position and it is comfortable for the patient. However, when the patient is on her back, just a 5 degree lateral tilt of the table will accomplish the same effect as far as vena caval pressure is concerned and this is particularly helpful at the time of cesarean section for abruptio placentae. During delivery in the lithotomy position, either a slight lateral tilt or, if that is not possible, an elevation of the head of the table will be of help. During labor and even throughout the prenatal period, the patient should be encouraged not to rest on her back.

Amniotomy. Early artificial rupture of membranes in all patients in early labor if conditions are suitable is the next point to which I would like to give some consideration. Although such a procedure might not prevent all cases of amniotic fluid embolism, it would produce an opening in the amniotic sac through which the fluid could leak out safely through the cervix, thus reducing the intrauterine pressure. It is true, however, that there might be sufficient amniotic fluid trapped behind the fetal head so that the procedure would be of little value. However, the advantages in those cases in which it works are obvious. It may prevent the acute and massive amniotic fluid embolism which results in shock and respiratory distress. Although these dramatic acute episodes are rather startling, according to Stone and associates,²⁶ the actual entry of amniotic fluid into the uterine vessels may not be too rare and subclinical forms of amniotic fluid infusion may occur quite frequently. Should this occur in a situation where there is an ABO incompatible mating, there is over a 50 per cent chance of A or B isoimmunization because of the A or B antigen content of the fluid. The well-known association of hypofibrinogenemia and amniotic fluid infusion need not be fully discussed here. Nilsen¹⁸ reported a case recently in which the patient's blood did not coagulate until after artificial rupture of the membranes. Accord-

ing to Posner and associates,²² artificial rupture of the membranes in abruptio placentae relieves intrauterine pressure and thus the risk of forcible entrance of more thromboembolic substances into the maternal circulation is diminished. One might, therefore, speculate as to the role of early amniotomy in the prevention of terminal abruptions.

Management of the umbilical cord. The management of the umbilical cord between the second and third stages of labor deserves some consideration. It has been stated that, in ancient times, the usual sequence of events was: (1) birth of offspring, (2) birth of the placenta, and (3) chewing off of the cord. In the usual normal delivery today, after the baby is born, it is placed slightly lower than the mother, usually some delay is permitted before the cord is clamped, or the cord is "milked" toward the infant, and then it is clamped and cut. Why the maternal side of the cord is clamped is difficult to answer unless the possibility is being considered that it is in common with the circulation of a second baby in the case of twin pregnancy. When the maternal side is clamped, after a few contractions, the fetal blood still contained in the placenta occasionally comes under some tension. This could force fetal blood through the torn chorionic villi into the retroplacental clot and thus into the uterine vessels. Many years ago, milk injected into the umbilical vein was found in the uterine veins. These exchanges and proofs of them were reviewed in 1955 by Rucknagel and Chernoff.²⁴ To make matters worse, in potential Rh incompatible infants we are instructed to clamp the cord immediately and not be concerned about getting the last amount of this sensitized blood into the infant. With larger amounts of fetal blood remaining in the placenta and attached cord, the chances of increased tension are greater. In addition, there is some delay in delivery of the placenta because cord blood specimens are obtained for typing and the Coombs test. This procedure probably does not help the prognosis of succeeding pregnancies.

Oxytocics. The final factor to be consid-

ered is the recent and more liberal use of oxytocics before the completion of the third stage of labor. In view of all the foregoing discussion, although the effects of the use of intravenous dilute Pitocin in the first stage of labor should be reconsidered, it may even be of more importance to re-evaluate the use of high doses of oxytocics with the delivery of the anterior shoulder. It is generally felt and confirmed by studies that the immediate blood loss is less with the use of oxytocics in the second stage of labor. However, the question which should be investigated is whether the initial good result might be a false impression. Bleeding might be initially controlled by a strong contraction but greater amounts of thromboplastic substances may be forced into the maternal circulation resulting, after the oxytocic effect has decreased, in constant, heavier than usual amounts of bleeding which, over a period of hours, could add up to much more than the initial loss would have been if the drug administration has been delayed until after the third stage of labor. Since the amount of bleeding at any one time would be within the upper limits of normal, the over-all increase would go unreported.

Summary and conclusions

Various factors which may increase or decrease the passage of large protein molecules across the maternal-fetal barrier have been discussed. Since the immediate and future obstetric results can be improved by limiting such transfer of substances to a minimum, this should be our goal when rendering obstetric care. The following procedures are recommended in order to obtain this goal. Some are based on factual evidence and others, although theoretical, are harmless. The list is by no means complete but

represents procedures not universally practiced for the purpose of obtaining the goals being considered in this discussion.

1. Prenatal care should begin as early as possible so that the implantation stage can proceed under optimum conditions. Liberal use of ascorbic acid and the bioflavonoids is recommended.

2. When broad-spectrum antibiotics are necessary, the use of vitamin K is recommended. Indication for antibiotics should be definite.

3. Maternity patients should be encouraged to sleep on their sides rather than on their backs during the entire pregnancy and when in labor. Consideration should be given to the position of the patient at the time of delivery.

4. Immediate artificial rupture of the membranes should be performed as soon as it can safely and conveniently be accomplished after the onset of labor. Good judgment, however, should be exercised, with basic obstetric principles used to determine when amniotomy is contraindicated.

5. The maternal side of the umbilical cord should never be clamped but rather be allowed to drain unless the possibility of multiple pregnancy is being considered.

6. Except for the use of very dilute Pitocin infusion, perhaps a return to the use of oxytocics only after the delivery of the placenta should be investigated. It should be evaluated not only on the basis of bleeding in the first hour after delivery but also on the amount of bleeding in the entire first 24-hours post partum. As yet not investigated is the difference in rise of anti-A or anti-B titers in the presence of A or B heterospecific pregnancies in those patients given oxytocics with delivery of the anterior shoulder and those in which the use of oxytocics is delayed until the placenta is delivered.

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Reviews | Abstracts

Edited by

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Selected abstracts

Canadian Medical Association Journal

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Carroll, J. J.: Anaesthesia for Obstetrical Manoeuvres and Operations, p. 184.
Moore, B. P. L., McIntyre, J., Brown, F., and Read, H. C.: Recognition of the Rare RH Chromosome D—A New Family Study, p. 187.

Irish Journal of Medical Science

No. 404, August, 1959.

McCarthy, John R.: Anoxia in the Newborn, p. 343.

Journal of Pediatrics

Vol. 56, January, 1960.

*McElfresh, A. E., Kurkcuoglu, M. Vaughan, V. C., III, and Armbruster, R.: Elution of Anti-A and Anti-B Antibody From Erythrocytes of Incompatible Newborn Infants, p. 39.
*Sisson, T. R. C., and Whalen, L. E.: The Blood Volume of Infants. III. Alterations in the First Hours After Birth, p. 43.
*Page, O. C., Garland, J., Stephens, J. W., and Hare, R. L.: The Electrocardiogram in Infants of Diabetic Mothers, p. 66.
McElfresh et al.: Elution of Anti-A and Anti-B Antibody From Erythrocytes of Incompatible Newborn Infants, p. 39.

The authors attempted to prepare eluates from the cord blood of infants whose blood type (A or B) was incompatible with that of their mothers (O). It was possible to elute homospecific antibody from the red cells of only 13 per cent of the infants studied. Only one third of the infants with a positive eluate had clinical evidence of hemolytic disease.

*These articles have been abstracted.

The majority of the infants in whom positive eluates were found had no jaundice, and a third of the infants in whom eluates could not be found were jaundiced. Therefore, the authors conclude that, "the ability to elute antibody from the red blood cells of the infant . . . must be concluded to be of no value in the prediction or confirmation of hemolytic disease due to A or B incompatibility."

S. G. Kohl

Sisson and Whalen: Blood Volume of Infants, p. 43.

Plasma volume increased 20 per cent, red cell mass 26 per cent, and total blood value 23 per cent in the first few hours after birth. These changes indicate that "caution should be used in producing an artificial expansion of the neonatal blood volume. Interference with these hemodynamic changes by effecting a transfusion of placental blood seems unwise; the hazards outweigh the rather uncertain benefits."

The authors postulated that the average increase of blood/volume (62 ml.) was due to an initial "sequestration" of blood in viscera and the lower parts of the body. This blood was introduced into the circulation as the permanent "vascular and pulmonary patterns" were established.

S. G. Kohl

Page et al.: Electrocardiogram in Infants of Diabetic Mothers, p. 66.

Twenty-one newborn infants of diabetic mothers were subjected to extensive electrocardiographic study. The authors conclude from their "small" series, that "abnormal electrocardiograms are uncommon in newborn infants of diabetic mothers."

S. G. Kohl

**Journal of the
Philippine Medical Association**

Vol. 35, December, 1959.

*Sta. Cruz, J. Z.: The Pathological Diagnosis of Choriocarcinoma From Endometrial Scraping, p. 805.

Sta. Cruz: Pathological Diagnosis of Choriocarcinoma From Endometrial Scraping, p. 805.

The author reviewed 3,802 endometrial scrapings obtained during the 10 year period 1945-1955. The incidence of chorioma was 183 cases (4.8 per cent), of which 93 were hydatidiform mole, 57 were chorioadenoma destruens, and 33 were choriocarcinoma.

The percentage of error in diagnosis from endometrial scrapings was as follows: 5 cases which were diagnosed as hydatidiform mole on curettings were found to be chorioadenoma destruens at hysterectomy—an error of 5.3 per cent. Six cases diagnosed as chorioadenoma on curettings were choriocarcinomas on hysterectomy, an error of 10.5 per cent. Two cases diagnosed as chorioadenoma on curettings were later found to be syncytial endometritis, an error of 2.2 per cent.

The author states the morphologic appearance of the cells themselves remains his main criterion for malignancy. In chorioadenoma destruens he looks for an irregularity of the trophoblastic layer in the periphery of the villus but, irrespective of the malignancy of the trophoblasts, the presence of intact chorionic villi makes the diagnosis chorioadenoma destruens or malignant mole. His criterion for diagnosis of chorionepithelioma in endometrial scrapings is the finding of anaplastic reaction of the trophoblastic cells with all the pleomorphic and mitotic nuclear changes.

Richard J. Calame

Lancet

Vol. 2, Sept. 5, 1959.

*Nilsson, I. M., Bergman, S., Reitalu, J., and Waldenstrom, J.: Hemophilia A in a "Girl" With Male Sex-Chromatin Pattern, p. 264.

*MacRae, D. J.: Monitoring the Heart of the Fetus and the Newborn, p. 266.

Nilsson et al.: Hemophilia A in a "Girl" With Male Sex-Chromatin Pattern, p. 264.

Although hemophilia (antihemophilic globulin deficiency) is transmitted by a sex-linked recessive gene, four instances of homozygous hemo-

philia resulting from the marriage of a hemophiliac man to a woman who carried the disease have been reported. Also, the homozygous female dog has been found to have hemophilia. However, additional instances of apparently classical hemophilia have been reported previously in a girl of 2 years who had an unknown family history and in a girl of 11 years who had a negative family history. These latter seeming exceptions to strict sex-linkage have not been explained although Quick and Hussey (*Lancet* 1: 1294, 1958) suggested a possible mutation.

The present report is concerned with a female child of 16 months who had always bruised easily and who had developed large hematomas which on one occasion caused the hemoglobin to fall from 11.2 Gm. per 100 ml. to 4.6 Gm. The child's mother was a known carrier of hemophilia A whose anti-hemophilic globulin activity (AHG) was 25 per cent. The child's father was normal (AHG 115 per cent) without any family history of hemophilia. The child's coagulation time was prolonged to 120 minutes. The plasma AHG activity as determined by the recalcification method on hemophilia A plasma was 0.1 per cent. The hemophilia B factor content of the plasma was 60 per cent. These and other laboratory findings were identical with those obtainable in severe hemophilia A in males.

Sex determination by means of studies of blood films and resting cells from skin were thought to indicate a male chromosomal pattern. Tissue cultures of skin showed 46 chromosomes and a probable XY sex chromosomal constitution. Inasmuch as none of the evidences of Turner's syndrome, such as digital abnormalities, webbed neck, heart disease, etc., were present in the patient, the genetic constitution XO seemed unlikely. It is possible, therefore, that seeming exceptions from sex-linked inheritance may in reality conform to the genetic pattern that would be expected.

David M. Kydd

MacRae: Monitoring the Heart of Fetus and Newborn, p. 266.

A device consisting of a sensitive small microphone that can be strapped to the abdomen of a pregnant woman and a selecting and amplifying sonoscope is described. The impulses may be made to activate a loud-speaker, earphones, a flashing light, or a recording device. Continuous monitoring of the fetal heartbeat has proved useful in providing early evidence of fetal dis-

tress. The device may also be used for monitoring the heartbeat in newborn infants.

David M. Kydd

Oct. 24, 1959.

*Chanarin, I., MacGibbon, B. M., O'Sullivan, W. J., and Mollin, D. L.: Folic-Acid Deficiency in Pregnancy—The Pathogenesis of Megaloblastic Anemia of Pregnancy, p. 634.

Chanarin et al.: Folic-Acid Deficiency in Pregnancy, p. 634.

Folic acid tolerance tests were carried out on the following groups of women: (A) 30 healthy nonpregnant women between the ages of 18 and 40; (B) 250 women without anemia who had been pregnant for varying periods; (C) 11 patients with normal twin pregnancies; (D) 11 patients with untreated megaloblastic anemia of pregnancy. The serum folic acid was determined 3, 15, and 30 minutes after the test dose of 15 µg of folic acid per kilogram of body weight had been injected intravenously. In Group A the mean values obtained at these three times were 131 ± 6 , 43 ± 3 , and 21 ± 4 µg per milliliter, respectively. In Group B before the twelfth week of pregnancy these values were already significantly lower, being 104 ± 8 , 28 ± 2 , and 11 ± 1 , respectively. In normal pregnancy the rate of clearance became progressively more rapid until by the thirty-sixth week the values at these same intervals of time became 84 ± 13 , 17 ± 1 , and 4 ± 0 µg per milliliter. At full term, although still rapid, it was somewhat slower than at 37 to 40 weeks and still slower in 9 women who were tested 3 to 5 weeks after their expected date of delivery. The difference between these last two groups was not statistically significant. In Group C the clearance of folic acid was more rapid in every instance of twin pregnancy, and in 3 instances no folic acid at all was found in the plasma 15 minutes after the injection. The most rapid clearance of folic acid occurred in Group D. In these patients with megaloblastic anemia the concentration of folic acid 3, 15, and 30 minutes after the injection were found to be 42 ± 11 , 2 ± 1 , and 0 µg per milliliter. In uncomplicated single pregnancy the rate of clearance was rapid but never as low as in megaloblastic anemia and not often as low as in twin pregnancy.

The absorption of folic acid was tested by determining the plasma levels of folic acid 1 and 2 hours after the oral administration of 40

µg of folic acid per kilogram of body weight in the following groups: (E) 90 healthy subjects of both sexes; (F) 45 women who were between 20 and 40 weeks pregnant; (G) 10 women with treated megaloblastic anemia in pregnancy. In Group E the peak mean value was 95 ± 9 µg per milliliter (range 42 to 186); in F the peak mean value was 48 ± 3 (range 11 to 86); and in G the peak mean value was 37 ± 6 (range 10 to 60). Two patients with megaloblastic anemia of pregnancy were retested 3 months after delivery and in both the absorption of folic acid had returned to normal.

The fact that the clearance of folic acid is more rapid in twin pregnancy and that in single pregnancy the rate of clearance increases in a comparable fashion to the increment of growth of the fetus suggests that deficiency of folic acid may result from increased fetal demand. The especially poor absorption test that was demonstrated in patients with megaloblastic anemia suggests that impaired absorption of folic acid may be of importance in the development of this condition.

David M. Kydd

Oct. 31, 1959.

*Oliver, M. F., and Boyd, G. S.: Effect of Bilateral Ovariectomy on Coronary-Artery Disease and Serum-Lipid Levels, p. 690.

Oliver and Boyd: Effect of Bilateral Ovariectomy on Coronary-Artery Disease and Serum-Lipid Levels, p. 690.

Of 31 women between 42 and 58 years of age who had had a unilateral ovariectomy 20 or more years previously one had evidence of coronary artery disease (3.2 per cent) whereas of 36 women between 37 and 58 years of age who had had a bilateral ovariectomy 20 or more years previously 9 had evidence of coronary artery disease (25 per cent). The latter group included one woman of 41 who died of a coronary infarction 11 years after the operation. The low incidence compares with an incidence of 3.5 per cent among 237 unoperated women between the ages of 45 and 59 in a general practice in Edinburgh and an incidence of 1.8 per cent found in 1,502 women between the ages of 40 and 59 in Framingham. Associated with the increased incidence of coronary artery disease among the women who had had a bilateral ovariectomy the mean serum cholesterol concentration in this group was 251 ± 43 mg.

per 100 ml. whereas it was 217 ± 56 mg. per 100 ml. in the group of women who had had a unilateral ovariectomy. Although a subtotal or total hysterectomy had been performed in all the patients from whom both ovaries had been removed the effect of hysterectomy alone could not be assayed because of the rarity of an isolated hysterectomy before the age of 35. Despite this the evidence suggests that ovarian estrogen secretion seems to be inversely related to the development of coronary artery disease and to elevated serum lipid levels. Bilateral ovariectomy seems to decrease the usual ratio of male/female found in the development of coronary artery disease below the age of 50. That bilateral ovariectomy should not be performed in young women unless absolutely necessary and that the use of estrogens until the age of 50 should be considered in patients where ovaries have been removed are precepts that are stressed.

David M. Kydd

Nov. 14, 1959.

*Pickett, M. T., Kyriakides, E. C., Stern, M. I., and Sommerville, I. F.: Urinary Pregnaneetriol Throughout the Menstrual Cycle, p. 829.

Pickett et al.: Urinary Pregnaneetriol Throughout Menstrual Cycle, p. 829.

Pregnaneetriol (5β - 3α : 17α : 20α -triol) is present in the urine of healthy men and women and is excreted in large amounts in the urine of patients with adrenocortical hyperplasia. In this study the excretion of pregnanediol and pregnaneetriol was determined throughout the menstrual cycle of a healthy woman of 26 years. The cyclic variations of the 2 substances roughly paralleled one another. The excretion of pregnaneetriol varied from 0.4 mg. per 24 hours during the follicular phase to 1.9 mg. per 24 hours during the luteal phase. Pregnanediol varied from 0.5 to 8.8 mg. per 24 hours during the same interval. The excretion of these substances was also determined during the menstrual cycle of an adrenalectomized woman of 45 years who was receiving prednisone and 9α -fluorohydrocortisone. This subject also showed increased pregnaneetriol and pregnanediol excretion during the second half of the cycle although the amounts were considerably smaller than in the healthy subject. The pattern of urinary pregnaneetriol excretion in both of these subjects suggests the possibility that this steroid may

have ovarian as well as adrenocortical precursors.

In a healthy young woman of 18 years who was studied $2\frac{1}{2}$ years after the menarche only small amounts of urinary pregnanediol were excreted. Urinary pregnaneetriol excretion was low also and there was no sustained increase in either steroid during the cycle in the young nulliparous woman.

David M. Kydd

Nov. 21, 1959.

Way, S., Hetherington, J., and Galloway, D. C.: Simultaneous Cytological Diagnosis of Cervical Cancer in Three Sisters, p. 890.

Vol. 1, Jan. 2, 1960.

*Johnston, J. A. L., and Liggett, S. W.: Pregnancy After Tuberculosis of the Fallopian Tubes, p. 24.

Johnston and Liggett: Pregnancy After Tuberculosis of Fallopian Tubes, p. 24.

An instance is reported of a patient aged 25, whose mother had renal tuberculosis, who developed irregular vaginal bleeding and lower abdominal pain. On operation she was shown to have uterine fibroids and tuberculosis of the Fallopian tubes. Tubercle bacilli were cultured from the pus found in the tubes. Subsequent to the operation she developed fever, pain in the chest, hemoptysis, and a pleural friction rub. This may have been a pulmonary infarct but because of the possibility of tuberculosis (despite 3 negative sputum examinations) treatment with streptomycin and isoniazid was started. The abnormalities in the chest subsided but evidence of a small amount of fluid in the chest persisted for 3 weeks. The fever disappeared except during the progestational phase of the menstrual cycles after 3 months. Antituberculosis therapy was continued. Eleven months after the first operation she became pregnant but aborted at 10 weeks. Convalescence was normal except that she developed thrombophlebitis. Fifteen months after treatment was started streptomycin was discontinued and the dose of isoniazid and para-amino-salicylic acid was diminished. She discontinued all therapy after 17 months. Two months later she again became pregnant. Because of the previous miscarriage 6 (25 mg.) of progesterone were implanted deep to the fascia lata and the administration of para-aminosalicylic acid was started again. Aside from some swelling of the right leg, transient albuminuria, and a rise in

blood pressure to 140/90, the pregnancy proceeded normally. Labor started spontaneously but, because of uterine inertia and nonengagement of the head, a normal infant who weighed 10 pounds was delivered by cesarean section. On the tenth postoperative day while up and about the patient suddenly collapsed and died from a pulmonary embolus.

Despite the patient's unfortunate death her history shows that radical surgical treatment of tuberculosis salpingitis is not always necessary nor does the disease necessarily result in sterility. At the time of the cesarean section neither Fallopian tube showed macroscopic signs of inflammation.

David M. Kydd

Jan. 9, 1960.

*Gosset, I. H.: A Perspex Icterometer for Neonates, p. 87.

*Cully, P. E., Waterhouse, J. A. H., and Wood, B. S. B.: Clinical Assessment of Depth of Jaundice in Newborn Infants, p. 88.

Gosset: A Perspex Icterometer for Neonates, p. 87.

A device was developed which consisted of a curved piece of transparent Perspex $\frac{1}{8}$ inch thick, $1\frac{1}{4}$ inch wide, and 7 inches long. On the convex surface toward the middle were painted 5 transverse stripes of slightly different but gradually more intense shades of yellow. These stripes and spaces between were each $\frac{3}{5}$ inch wide. In use the instrument was pressed against the baby's nose until the skin blanched and the yellow color of the skin matched with the yellow stripes on the scale. With the shades of color used (Robbialac Colorizer paint No. 501, shades A, B, C, D, and E), the results obtained by means of the device correlated roughly with the level of bilirubin found in the infant's sera although, as might be expected, there was a considerable scattering of values. However, the instrument proved of value in indicating which babies should be subjected to serum bilirubin estimations and also in rapidly estimating whether the jaundice was decreasing or increasing toward the critical levels of 24 mg. per 100 ml. at which point replacement transfusions were undertaken. The device is simple but has disadvantages such as unreliability in artificial light and on bruised noses, and it has limited use in the non-white races. A more important disadvantage is that when jaundice is developing rapidly the color of the skin may lag behind the actual

amount of bilirubin in the serum. Hence, babies developing jaundice within 36 hours of birth should always have the serum bilirubin level determined, since to rely on this instrument under this condition would be dangerous.

David M. Kydd

Cully, Waterhouse, and Wood: Clinical Assessment of Depth of Jaundice in Newborn Infants, p. 88.

With use of the icterometer described by Gosset (*Lancet* 1: 87, 1960), 183 observations were made on 165 babies who were jaundiced. The stripes of yellow paint on the instrument employed were of such a shade that stripe No. 2 was found to correspond to a mean serum bilirubin of 5.55 ± 1.61 (range 3.9) mg. per 100 ml., stripe No. 3 to 10.03 ± 2.26 (range 10.1), and stripe No. 4 to 15.73 ± 3.03 (range 11.7) mg. per 100 ml. Despite the range of values, this simple instrument, which can be carried in the pocket and washed after use as one washes one's hands, was useful in detecting jaundice. At an icterometer reading of 3 only 1 per cent of cases with an indirect level of serum bilirubin of 16 mg. per 100 ml. or more will be missed. Except in infants with rapidly increasing jaundice during the first day of life (such as in Rh incompatibility) if the icterometer reading is 3 or below the determination of serum bilirubin levels might safely be omitted whereas above this level blood studies must be undertaken.

David M. Kydd

Jan. 16, 1960.

Mullins, Ann: Overweight in Pregnancy, p. 146.
Court Brown, W. M., Jacobs, P. A., and Doll, R.: Interpretation of Chromosome Counts Made on Bone-Marrow Cells, p. 160.

Jan. 23, 1960.

*Dalton, Katharina: Early Symptoms of Pre-eclamptic Toxemia, p. 198.
Dalton: Early Symptoms of Pre-eclamptic Toxemia, p. 198.

In a group of 633 patients who were between 16 and 28 weeks pregnant, 491 (78 per cent) stated that they felt well and 142 (22 per cent) had symptoms (nausea, vomiting, headaches, vertigo, fainting, paresthesia, lethargy, or depression). None of this latter group had hypertension, edema, or albuminuria at the time of questioning but 25 per cent of these women

later developed toxemia whereas only 10 per cent of the patients who stated that they felt well subsequently developed toxemia. The mere fact of feeling unwell appeared to be of more importance than the occurrence of any one specific symptom, or group of symptoms inasmuch as there was little difference in the symptoms of those who afterward developed toxemia and those who did not. These women did not complain lightly for 94 per cent had at least 2 unrelated symptoms, 71 per cent had 3, and 48 per cent had at least 4. Persistence of symptoms was of even greater significance for, of 74 patients with symptoms on only one occasion, 20 per cent developed toxemia whereas, of 17 patients whose symptoms persisted from one interview until the next, a month later, 41 per cent developed toxemia. Patients with these non-specific symptoms during the middle trimester had a much higher incidence of severe toxemia, albuminuria, stillbirth, and twins than did those who felt well. The suggestion is made that patients with symptoms during pregnancy be treated with a toxemic prophylactic regimen even in the absence of signs or excessive weight gain.

David M. Kydd

Münchener medizinische Wochenschrift

Vol. 101, July 31, 1959.

McCrea, L. E.: A New Aspect of Innervation of the Urinary Bladder and Its Relation to Bladder Function Following Extensive Pelvic Surgery, p. 1283.

Murano, C.: Prophylaxis of Kernicterus With Corticosteroids, p. 1292.

Guimbretiere, J., Harousseau, H., Delaroche, Y., and Heilmann, E. M.: Heparinized Fresh Blood for Exchange Transfusion in the Newborn, p. 1297.

Aug. 14, 1959.

Dontenwill, W., Ranz, H., and Mohr, U.: The Import of Necrosis as Cause of Blood Protein Changes in the Presence of Tumors, p. 1365.

Soost, H.-J., and Pichlmayr, R.: Parallel Investigation of Fixing Methods for Cytological Specimens Which Are to Be Shipped, p. 1368.

Sept. 4, 1959.

Mey, R.: Habitual Late Abortion Due to Incompetent Cervix and Its Surgical Management, p. 1484.

*Wolffram, E.: Experience With the New Anti-Emetic "Postafene" in Gynecology, p. 1494.

Breitner, J.: Newer Approach to Prenatal Care, p. 1497.

Keuth, U.: Nil Nocere! Errors in Diagnosis in Erythroblastosis Neonatorum, p. 1500.

Wolffram: Experience With the New Anti-Emetic "Postafene" in Gynecology, p. 1494.

Postafene rectal suppositories (meclizine, 25 mg., and hydroxyzine, 25 mg.) was used for vomiting in 210 women with 95 per cent success. The series included 32 patients with hyperemesis of varying degree, 102 women with radiation sickness, 73 cases of postoperative nausea and vomiting, and 3 patients with nausea and vomiting due to idiosyncrasy to sulfonamides.

Walter F. Tauber

Sept. 11, 1959.

Hartenbach, W.: Diagnosis and Management of Cushing's Syndrome, p. 1560.

Mainzer, F.: Placebo-Effect of Surgical Intervention, p. 1572.

Oct. 16, 1959.

*Hohlbein, R., and Krimmenau, R.: The Values of Certain Diagnostic Procedures in Evaluating Atypical Cervical Epithelium, p. 1824.

Hohlbein and Krimmenau: Values of Certain Diagnostic Procedures in Evaluating Atypical Cervical Epithelium, p. 1824.

In 27 biopsies of the cervix, the lesion was missed in 9 patients (33 per cent). Pathologic tissue remained behind only in 16 of 135 patients (11.9 per cent) after conization. Effective conization requires inclusion of the entire atypical area, as well as two thirds of the cervical canal. In view of the figures obtained, conization is presented as the method of choice in evaluating atypical cervical epithelium.

Walter F. Tauber

Proceedings of Society for Experimental Biology and Medicine

Vol. 103, January, 1960.

*Lostroh, A. J.: In Vitro Response of Mouse Testis to Human Chorionic Gonadotropin, p. 25.

*Herrmann, W. L., Schindl, I. K., and Bondy, P. K.: Effect of Estrogen on Steroid Levels in Plasma and Urine, p. 103.

*Adamis, D. M.: Rapid Method for Determination of Plasma Fibrinogen, p. 107.

Lostroh: In Vitro Response of Mouse Testis to Human Chorionic Gonadotropin, p. 25.

Studies were undertaken to determine the growth and response of mouse testis in in vitro culture media.

Testes from mice 3 days of age were cultured in an in vitro system for 7 to 14 days on described culture media. After 7 days of culture, tubular size decreased and interstitial cell cytoplasm decreased. These degenerative changes were ameliorated with the addition of HCG to the culture media. The addition of HCG enhanced the secretion of androgen for 14 days under in vitro conditions.

Lawrence J. Sonders

Herrmann, Schindl, and Bondy: Effect of Estrogen on Steroid Levels in Plasma and Urine, p. 103.

The present study investigated the effects of physiologic levels of naturally occurring estrogenic material on the adrenal steroid levels in plasma and urine and also determined ACTH responsiveness under these conditions. The experiment revealed that plasma levels of hydrocortisone remained unchanged after estrogen administration and there was no significant difference in response to ACTH with or without estrogen. There was a decreased urinary resting level of the 17-hydroxy steroids after estrogen administration and the response to ACTH plus estrogen was less than to ACTH alone. Urinary pregnanetriol excretion was diminished after estrogen administration and levels were lower after ACTH plus estrogen than with ACTH alone.

It has been shown that while the administration of estrogen did not affect the plasma levels of adrenal steroids nor their response to ACTH infusions, the excretion of adrenal steroids is significantly decreased. The authors feel that although this may represent interference with the biosynthesis of these products by estrogen, a more attractive theory is that of a delayed catabolism brought about by increased protein-binding as occurs with hydrocortisone.

Lawrence J. Sonders

Adamis: Rapid Method for Determination of Plasma Fibrinogen, p. 107.

A technique to determine the level of plasma fibrinogen rapidly and without loss of accuracy

is presented. The method outlined involves: (1) the preparation of a substrate reagent of defibrinated plasma which may be stored indefinitely, (2) the preparation of plasma to be tested in buffered dilutions, (3) the test utilizing the plasma to be tested, substrate reagent, CaCl_2 , and rabbit brain thromboplastin which gives clotting time in seconds, (4) the comparison of the determined clotting time in seconds with an accurate graph which correlates clotting times with plasma fibrinogen percentage levels.

Lawrence J. Sonders

Wiener klinische Wochenschrift

Vol. 21, Oct. 23, 1959.

*Husslein, H., and Hofhansl, W.: The Possibilities of Artificial Delay in Menstruation, p. 821.

Husslein and Hofhansl: Possibilities of Artificial Delay in Menstruation, p. 821.

Artificial, pharmacologically induced delay in menstruation was produced in a total of 86 patients with a newly available oral estrogen, ethynodioltestosterone acetate in combination with ethynodiol and hydroxyprogesterone capronate. The indications for delaying menstruation included polymenorrheic syndromes together with elective delays based on the wish of the patients, some of whom wished to be free from menstruation during trips or vacations. The authors' data show that when the menstrual cycle could be accurately predicted in advance, delay in menstruation can be induced by the administration of appropriate combinations of estrogen, androgen and progesterone without any danger to the patient. The orally administered ethynodiol was a method which the authors preferred to the injection of estradiol benzoate in combination with hydroxyprogesterone capronate, requiring a much lower dosage and producing a much more predictable effect.

Douglas M. Haynes

Zentralblatt für Gynäkologie

Vol. 81, July 11, 1959.

Fuhrmann, K.: Colorimetric Determination and Histochemical Demonstration of Amino Peptidase in Tissues of the Female Genital Tract, p. 1105.

Aldea, A., Luca, V., and Filipescu, I.: Question on Pathogenesis and Therapy of Amenorrhea and Genital Tuberculosis, p. 1123.

July 18, 1959.

*Stark, G.: Cathepsine Activity in the Cellular Fraction of the Placenta in Toxemia and Postmaturity, p. 1142.

Szczepanik, E.: Pregnancy Complicated by Thrombosis of the Superior Mesenteric Artery, Case Report, p. 1145.

Topp, G.: Abortion and Sterility, p. 1148.

*Haller, J.: Clinical Experience With Synthetic Oxytocin in Obstetrics; Average Minute Dosage for Induction and Stimulation of Labor, p. 1153.

Baradlai Bank, E.: Our Method and Results in Homologous Artificial Insemination, p. 1161.

Stark: Cathepsine Activity in Cellular Fraction of Placenta in Toxemia and Postmaturity, p. 1142.

Cathepsine activity was determined in the placentas in 10 cases of toxemia and 6 cases of postmaturity of 2 weeks or greater. Fifteen normally pregnant women were used for controls. A 50 per cent reduction of the enzymes in the nucleus and mitochondria and a 10 per cent increase of the ferment in the cytoplasm was found in all toxemia and postmaturity placentas. No changes were found in whole tissue. It is suggested that disturbed cell function causes a change in activity.

Walter F. Tauber

Haller: Clinical Experience With Synthetic Oxytocin in Obstetrics, p. 1153.

Synthetic oxytocin was used in 455 patients for various obstetrical indications. It was found to be as efficacious as Pitocin. Since the synthetic is free of pressor principle, it is especially valuable. The rate of flow needed for induction varied from 0.0055 to 0.066 I.U. per minute, and from 0.025 to 0.04 I.U. per minute for stimulation in dyskinesia. In view of the large range of dosage requirements, the drug must be started very slowly and its administration closely supervised.

Walter F. Tauber

July 25, 1959.

Sander, M.: A Large Retroperitoneal Mesenchymoma of the Pelvis and Abdomen, Case Report, p. 1173.

Lange, H.: The Pathology and Management of Sarcoma of the Breast, p. 1180.

Niedner, K., Jäger, G.: The Treatment of Embolism and Anti-Coagulants in the Immediate Postoperative Period, Case Report, p. 1188.

*Wille, P.: The Meaning of Prothrombin, Antithrombin, and Fibrinogen in Shortening Coagulation Time During Operation and Anesthesia, p. 1195.

Waidl, E.: Development and Treatment of Uterine Inversion, Case Report, p. 1201.

*Wilken, H.: The Question of Rupture of the Uterus in Labor, p. 1205.

Wille: Meaning of Prothrombin, Antithrombin, and Fibrinogen in Shortening Coagulation Time During Operation and Anesthesia, p. 1195.

Based on 204 patients, it was determined that there is a generalized increased clotting efficiency during operations which aids hemostasis in the incision. This is not due to tissue thrombokinase liberated in the wound area. Anesthesia, even before any incision, caused an increase in clotting factors, which indicates that there is an autonomic influence on this. This finding is of importance for an understanding of thromboembolic complications.

The increased readiness to clot formation is associated with an increase in all factors of coagulation and a decrease in antithrombin activity. The increase of fibrinogen is particularly marked. It is suggested that fibrinogen is liberated from the liver during surgical procedures.

Walter F. Tauber

Wilken: Question of Rupture of Uterus in Labor, p. 1205.

Twenty-one cases of rupture of the uterus in labor were analyzed. These included 7 patients with rupture of an old uterine scar. Of particular note were 4 of these patients who had low cervical incisions. There were, further, 4 disproportions and 3 untreated transverse lies. Two had undergone previous trauma to the musculature (one curettage with perforation, one manual removal of placenta followed by sepsis). The remainder of the cases are ascribed to malpresentation, trauma, or stimulation of contractions. Maternal mortality occurred in 3 patients (14.3 per cent) including 2 who were admitted after rupture. The fetal mortality rate was 71.4 per cent. Postoperative maternal morbidity occurred in 28.6 per cent of cases.

Walter F. Tauber

Aug. 1, 1959.

Gasmann, W., and Lack, H.: Contribution on the Diagnosis of Pelvic Kidney, p. 1217.

Quaini, P., and Terzi, I.: The Relation Between Urinary Incontinence and Uterine Prolapse in Various Degrees, p. 1220.

*Becker, H.: Operation for Stress Incontinence With Assured Success, p. 1227.

Flämrich, E.: Surgical Closure of a Large Bladder Diverticulum Into the Vagina, Case Report, p. 1230.

Döderlein, G. G.: "Einroll" Plastic, p. 1236.

Becker: Operation for Stress Incontinence With Assured Success, p. 1227.

The author attaches the bladder and bladder neck to the uterus at the level of the peritoneal reflectum, after the usual freeing and advancing of the bladder. He reports 10 cases and requests further evaluation elsewhere with a larger series.

Walter F. Tauber

Aug. 8, 1959.

Ruck, C. J., and Parniske, A.: Synthetic Oxytocin in the Conduct of Labor, p. 1253.

Sturma, J.: Pregnancy and Delivery After Implantation of the Ovary into the Uterus, Case Report, p. 1260.

*Timonen, S., and Göltner, E.: The Import of "Hormone-Cytology" of the Vagina and Pregnanediol Excretion in the Urine for Prognosis in Threatened Abortion, p. 1263.

Vorster, R.: Hormone Ratio With Particular Attention to Tuberculosis in Pregnancy, p. 1271.

Timonen and Göltner: Import of "Hormone-Cytology" of Vagina and Pregnanediol Excretion in Urine for Prognosis in Threatened Abortion, p. 1263.

Hormone levels were examined cytologically and via pregnanediol excretion in 140 women with threatened abortion. Smears were unreadable in 10 per cent of the cases. Of the remainder, correct prognosis for untreated cases could be made by evaluation of the smear in 77.8 per cent.

A single pregnanediol determination led to correct prognosis in 89.2 per cent of cases. Combination of the methods and serial evaluation increased the accuracy to over 95 per cent.

Similarly, the effect of hormone therapy can be evaluated.

Walter F. Tauber

Aug. 15, 1959.

*Fekete, A.: The Importance of Hypotensive Symptom-Complex in Obstetrics and Gynecology, p. 1297.

Mink, E.: Neurotherapy of the Thyroid to Overcome Resistance to Therapy in Habitual Abortion, p. 1311.

Mohrmann, J. F.: Contribution on the Diagnosis of Erythroblastosis, p. 1318.

Kresse, H.: Abdominal Twin Pregnancy in the Fourth Month, Case Report, p. 1322.

Fekete: Importance of Hypotensive Symptom-Complex in Obstetrics and Gynecology, p. 1297.

The symptoms associated with hypotension include weakness, fatigue, vertigo, fainting, nausea, and vomiting. During menstruation they are caused by a premenstrual drop in hormone levels. Various autonomic centers react with varying speed. Thus, there is parasympathetic dominance from 2 days before to the first day of menses.

In early pregnancy, hypotensive changes can mimic ectopic pregnancy, probably because of intermediate metabolites.

In the middle trimester, blood pressure drops because of hemodynamic factors (reduced muscle tone, show return to the right side of the heart, and blood stagnation to some degree of blood behind the placenta with no immediate compensation in plasma volume).

In older women, even mild postoperative hypotension can cause cerebral changes in the presence of borderline arteriosclerosis.

Some cases of shock in labor are due to "atypical toxemia." In such cases artificial hibernation, sympathomimetics, and cortisone may be indicated, rather than transfusion.

Walter F. Tauber

Vol. 81, Aug. 22, 1959.

Elias, P., and Vago, O.: Classification of Intersexuality in Man, p. 1377.

Würterle, A., and Schmidt, W.: Hormone Determination in the Menstrual Cycle, p. 1389.

Seidenschnur, G.: The Use of "Ahypnon" as Barbiturate Antagonist in Minor Gynecology, p. 1397.

*Stambolovic, B., Mirjanic, N., and Jeric, S.: Mumps and Fertility in Women, p. 1400.

Stambolovic, Mirjanic, and Jeric: Mumps and Fertility in Women, p. 1400.

Between 1946 and 1957, 27 women with mumps during and after puberty were seen at the University of Belgrade. Follow-up showed no damage to ovulation. However, there was a reduction

in fertility, probably because of inflammatory changes of the Fallopian tubes.

Prior to their contracting the disease, these patients had a total of 14 deliveries and 18 non-spontaneous abortions. Afterward, there were only 4 and 7, respectively. Eleven of the patients were sterile. In 10 of them, an etiological connection to mumps could be assumed. Tube damage was evident in 7, including salpingo-oophoritis in 2, obstructed tubes in 3, and ectopic pregnancy in 2.

The conclusion is reached, therefore, that mumps is no more innocuous for women than it is for men.

Walter F. Tauber

Sept. 5, 1959.

Hohage, E., and Lau, H. U.: Observations on Spontaneous Change of Presentation Near Term, p. 1409.

*Rimbach, E., and Bonow, A.: Non-protein Nitrogen Following Delivery and in the Neonatal Period, p. 1418.

Menyasz, E., Fanea, E., Uza, E., and Ardeleanu, B.: Gangrene of the Hand Immediately Postpartum, p. 1424.

Hofmann, D.: Follow-up of Cancer Patients

After Radiation Therapy in Gynecology, p. 1428.

Margitay-Becht, M.: Prolapse of the Cervical Mucus, p. 1441.

Rimbach and Bonow: Non-protein Nitrogen Following Delivery and in the Neonatal Period, p. 1418.

A recent micro method has made it possible to determine NPN in the newborn. Parallel studies were made on 40 babies, evenly divided between above and below 3,000 grams, and on their mothers. Some of the babies were followed for 9 days. The smaller babies had a slightly higher azotemia at birth than the larger ones (average 27.7 mg. per cent and 25.5 mg. per cent, respectively). In both groups the mothers' NPN was about 10 per cent lower than the infants. The difference is probably due to concentration gradient across the placenta, rather than an active placental barrier. All babies showed a rise of NPN in the first 4 to 5 days of life, followed by a slow reduction. They had not reached the birth level by the ninth day. Although the series is small, it appears that the greatest increase occurs in babies who have been exposed to stress in utero near term (toxemia, fever, etc.).

Walter F. Tauber

Correspondence

Hand-Schüller-Christian disease and pregnancy

To the Editors:

The case report, "Hand-Schüller-Christian Disease and Pregnancy," by Duane B. Heilbronn and Don N. Ridgway (AM. J. OBST. & GYNEC. 79:805, 1960), leads off with the statement, "This case is reported because search of the literature has failed to produce a recorded case of coexistence of Hand-Schüller-Christian disease and pregnancy."

However, the review which the authors of the case report cite as Reference 1 (Avery, M. E., McAfee, J. G., and Guild, H. G.: AM. J. MED. 22:636, 1957) gives a brief account of just such a case. I quote from page 646 of the reference: "One patient in this series became pregnant in the course of her illness. Patient L. D. (No. 26) conceived six years after her initial lesion. During the third month of pregnancy diabetes insipidus developed and persisted after the delivery of a normal infant at term. She has had no subsequent pregnancies."

The number of patients in the childbearing years reported in the above-mentioned review appears to be 5—not 7 as stated in the case report. (See table, page 638 of the review.)

*George X. Trimble, M.D.
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April 9, 1960*

Preparation of Adrenalin-saline mixture

To the Editors:

I shall be glad to call your attention to a possible error in pharmacognosy which might occur from following the instructions mentioned for the preparation of "Adrenalin-saline" mixture outlined by Drs. Scott, Welch, and Blake in their article, "Bloodless Technique of Cold Knife Conization (Ring Biopsy)," on page 62 of the January, 1960, issue of the JOURNAL.

The directions call for adding 3 drops of Adrenalin to each ounce of saline. Several variables enter into determining what the final concentration of the mixture will be in addition to those listed, viz.: the strength of the initial Adrenalin solution and the actual volume of the drops which are to be added, commercially available solutions of Adrenalin varying from 1:100 to 1:10,000, and the number of drops per cubic centimeter of solution varying from 5 or 6 to about 40 using equipment routinely available in operating rooms. Thus a final concentration of Adrenalin too weak to be effective or so strong as to increase the incidence of side reactions could easily result.

The optimal concentration of epinephrine (Adrenalin) for the purpose of producing local vasoconstriction by infiltration has been determined to be 1:200,000 (Leser, A. J.: Anesthesiology 1: 205, 1940), and it is simply and accurately prepared by adding 0.5 ml. Adrenalin 1:1,000 from a 2 ml. syringe to 200 ml. normal saline. Increasing the concentration of Adrenalin beyond this limit sharply increases the incidence of toxic systemic reactions without yielding any appreciable additional local vasoconstriction.

That some systemic absorption of the drug injected into the highly vascular cervix occurs is not doubted by the vigilant anesthesiologist who frequently sees a resultant transient rise in blood pressure and pulse rate. In most subjects the absorption of minimal amounts of 1:200,000 epinephrine is well tolerated under Pentothal-nitrous oxide anesthesia but may be lethal under cyclopropane, trichlorethylene, chloroform, or Fluothane. Nevertheless, even under Pentothal-nitrous oxide, ether, or some regional anesthetic, individuals occasionally exhibit cardiac arrhythmias in response to 1:200,000 epinephrine when the absorption is fairly rapid as when injected partially or totally into a blood vessel. For this reason, one should always first exert a vacuum on the syringe in each of several quadrants while rotating the syringe to be reasonably certain that

the needle tip is not in a blood vessel. In the patient with a disturbance of the cardiac rhythm, Adrenalin should be used only after consultation with the anesthesiologist and the cardiologist to establish the nature of the arrhythmia, and the drug probably ought never be employed in the presence of ventricular arrhythmias for fear of ventricular fibrillation. The use of a sympathomimetic amine having no direct effect on the cardiac rhythm such as Neosynephrine in 1:200,000

might well be considered in patients afflicted with cardiac arrhythmias.

I sincerely hope that this information will be of value to the readers of the JOURNAL and that the occasionally tragic epinephrine reaction can be thus avoided.

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April 5, 1960*

Item

Certifications by American Board of Obstetrics and Gynecology

The following doctors were certified by the American Board of Obstetrics and Gynecology on April 15, 1960, when final certifications in this specialty were made.

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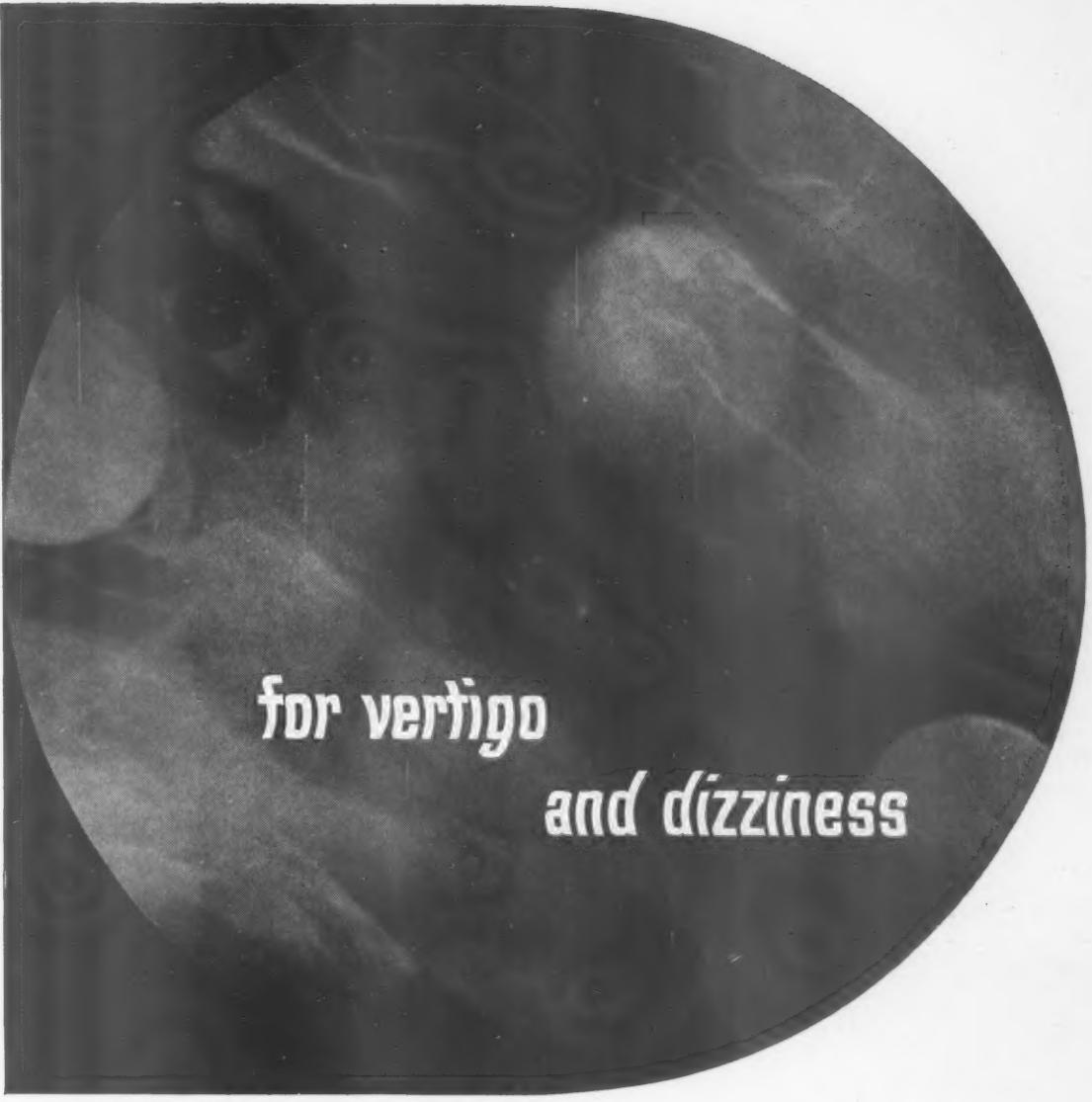
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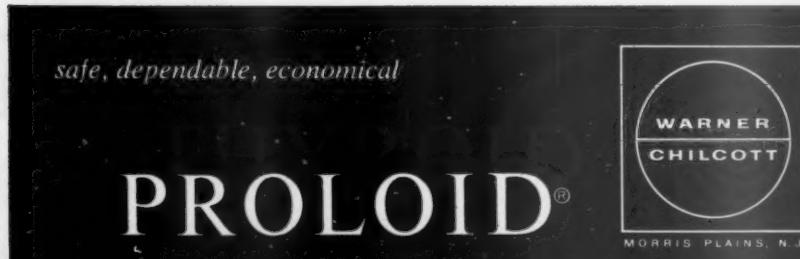
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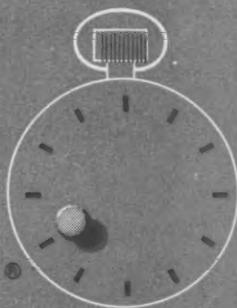
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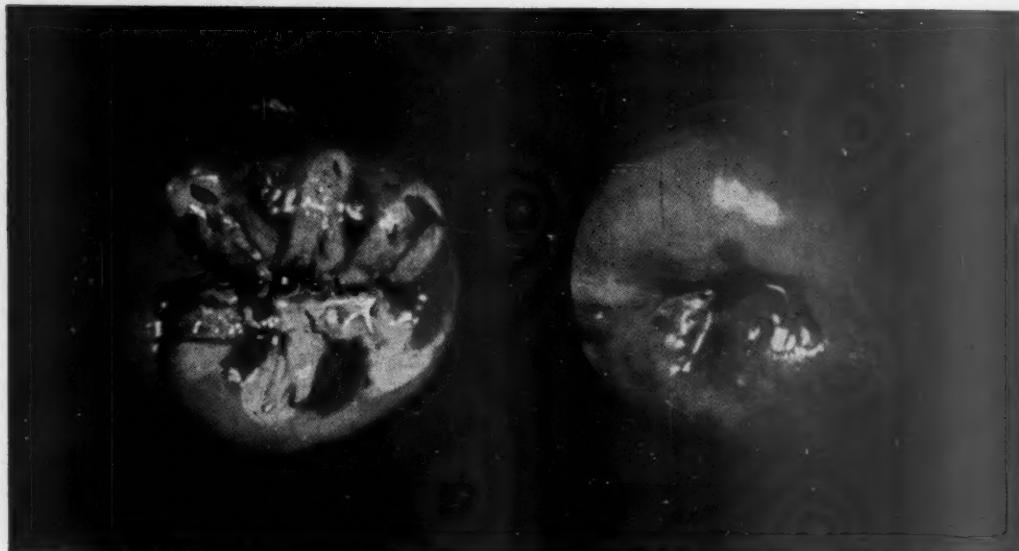
References: 1. Recent compilation of case reports received by the Medical Department, White Laboratories, Inc. 2. Ernst, E. M.: Clin. Med. (in press). Additional bibliography: Ayd, F. J., Jr.: Current Therap. Res. 1:41, 1959. Bodí, T., et al.: Clin. Res. 8:72, 1960. Dunlop, E.: Personal communication. Grimaldi, R.: Presented at Annual Congress of Pan-American Medical Association, May 6, 1960, Mexico City. Olson, J., and Carsley, S. H.: Personal communication.

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Fields, H.; Greene, J. W., Jr., & Franklin, R. R.: *Obst. & Gynec.* 13:353, 1959. 33560 PARKE, DAVIS & COMPANY · Detroit 32, Michigan

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1. Hayden, G. E.: Am. J. Obs. & Gynec. 76:271, 1958. 2. New & Nonofficial Drugs: J.A.M.A. 168:181, 1958. 3. Page, E. W.: GP 9:53, 1954.

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references: (1) Voulgaris, D. M.: Dysmenorrhea—Treatment with Isoxsuprine, *Obstetrics and Gynecology*, to be published. (2) Busky, A. H., to be published.

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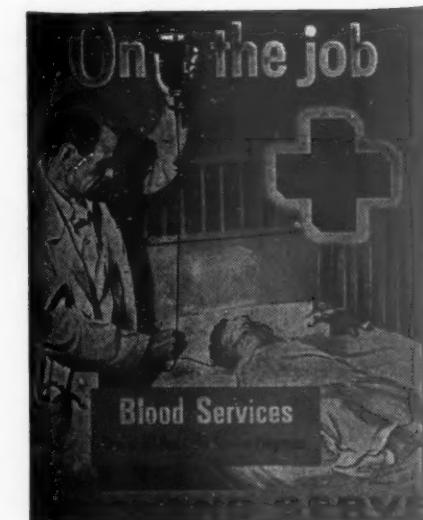
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1. Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953. 2. Javert, C.: Obst. & Gynec. 3:420, 1954.

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Bibliography: 1. Finegold, Wilfred J.: Internat. J. of Fertil. 3:143 1958
2. Palmer, A.: Internat. J. of Fertil. 4:365 1959



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1. Projection from Vital Statistics, U.S. Government Dept. HEW, Vol. 48, No. 14, 1958, p. 398.
2. Modell, W.: Drugs of Choice 1958-1959, St. Louis, C. V. Mosby Company, 1958, p. 347.



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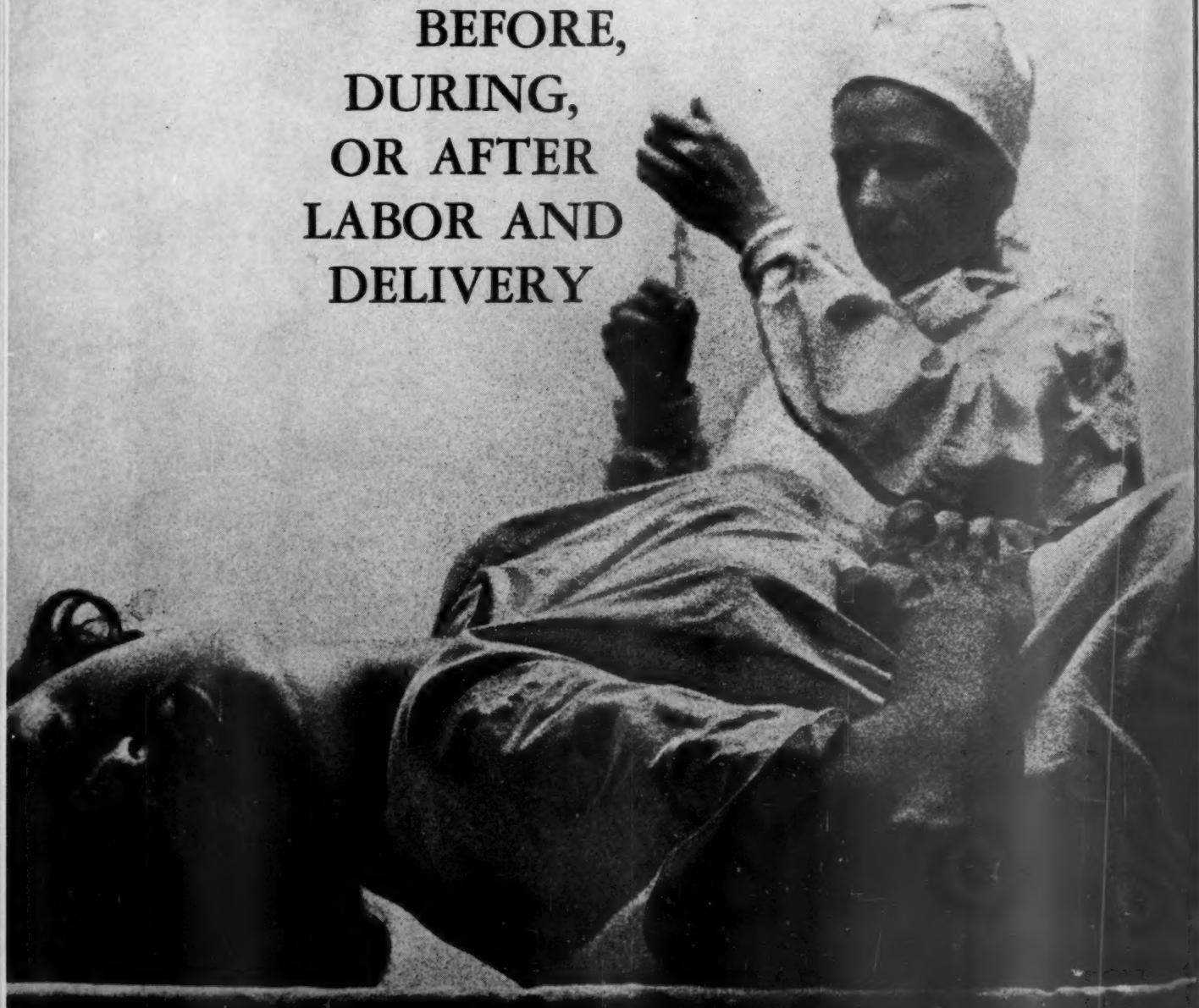
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OR AFTER
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Ensey, J. E.: Am. J. Obst. 77:185, 1959

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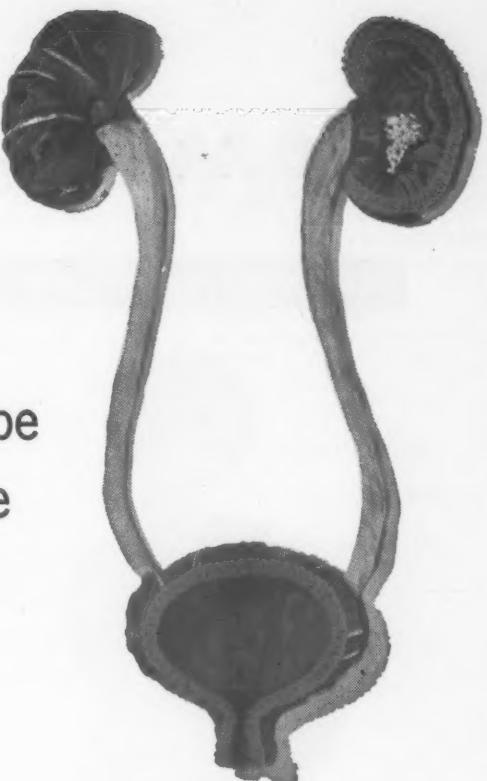
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REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1963.

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**gas is for balloons...
not for
pregnant
women**



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at bedtime

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alseroxylon, 2 mg.

...does more than lower blood pressure!

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Freedom from concern over sudden
hypotensive episodes or unwanted
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1. Wizenberg, M. J., et al.: Am. J. Obst. & Gynec. 78: 405 (Aug.) 1959.

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(anileridine)

effective even for
intense pain
parenterally or orally



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